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(54) Title: STEM CELL

(57) Abstract: There is provided a method to modulate the differentiation state of embryonic stem cells in culture by the providing ligands which bind receptors in the *Notch* and *Wnt* pathways.



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STEM CELL

The invention relates to a method to modulate the differentiation state of embryonic stem cells.

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During mammalian development those cells that form part of the embryo up until the formation of the blastocyst are said to be totipotent (e.g. each cell has the developmental potential to form a complete embryo and all the cells required to support the growth and development of said embryo). During the formation of the
10 blastocyst, the cells that comprise the inner cell mass are said to be pluripotent (e.g. each cell has the developmental potential to form a variety of tissues).

Embryonic stem cells (ES cells, those with pluripotentiality) may be principally derived from two embryonic sources. Cells isolated from the inner cell mass are
15 termed embryonic stem (ES) cells. In the laboratory mouse, similar cells can be derived from the culture of primordial germ cells isolated from the mesenteries or genital ridges of days 8.5-12.5 *post coitum* embryos. These would ultimately differentiate into germ cells and are referred to as embryonic germ cells (EG cells). Each of these types of pluripotent cell has a similar developmental potential with
20 respect to differentiation into alternate cell types, but possible differences in behaviour (eg with respect to imprinting) have led to these cells to be distinguished from one another. Hereinafter embryonic stem cells will encompass both these stem cell – types.

25 Typically ES cell cultures have well defined characteristics. These include, but are not limited to; maintenance in culture for at least 20 passages when maintained on fibroblast feeder layers; produce clusters of cells in culture referred to as embryoid bodies; the ability to differentiate into multiple cell types in monolayer culture; and express ES cell specific markers.

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Until very recently, *in vitro* culture of human ES cells was not possible. The first indication that conditions may be determined which could allow the establishment of human ES cells in culture is described in WO96/22362. The application describes cell lines and growth conditions which allow the continuous proliferation of primate ES cells which exhibit a range of characteristics or markers which are associated with stem cells having pluripotent characteristics.

More recently Thomson *et al* (1998) have published conditions in which human ES cells can be established in culture. The above characteristics shown by primate ES cells are also shown by the human ES cell lines. In addition the human cell lines show high levels of telomerase activity, a characteristic of cells which have the ability to divide continuously in culture in an undifferentiated state. Another group (Reubinoff *et. al.*, 2000) have also reported the derivation of human ES cells from human blastocysts. A third group (Shamblott *et. al.*, 1998) have described EG cell derivation.

A feature of ES cells is that, in the presence of fibroblast feeder layers, they retain the ability to divide in an undifferentiated state for several generations. If the feeder layers are removed then the cells differentiate. The differentiation is often to neurones or muscle cells but the exact mechanism by which this occurs and its control remain unsolved. It would be desirable to have a reliable culture system which does not require the presence of fibroblast feeder cells but includes the addition of a factor(s) which maintain ES cells in an undifferentiated state. A prerequisite to the successful exploitation of ES cells in tissue engineering is to provide a reliable and defined cell culture system which can be used to control the differentiation of ES cells into a selected cell-type. The identification of gene targets involved in maintaining ES cells as ES cells and the identification of gene targets involved in differentiation will facilitate this objective.

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We have identified a regulatory pathway involved in the mechanism by which ES cells are maintained as ES cells in culture and which also influences the differentiation of said cells in culture. The regulatory pathway comprises two families of genes referred to as *Notch* and *Wnt*.

5

The *Notch* gene is a *Drosophila* prototype for a family of homologues found in diverse species, encoding large, single-span, transmembrane receptors (reviewed in Weinmaster, 1997). Within the extracellular domain, located distally from the transmembrane region, are found multiple (10-36), tandem arrays of epidermal growth factor-like repeats (Wharton et al., 1985; Kopezynski et al., 1988). More proximally are found 3 cysteine-rich, Lin-12/Notch repeats and two conserved cysteine residues. The intracellular domain contains, from proximal to distal with respect to the transmembrane region, a subtransmembrane region (STR), six ankyrin repeats and a region rich in proline, glutamic acid, serine and threonine (PEST). The generic Notch structure is illustrated in Figure 1.

15

Wnt genes encode diffusible, extracellular signalling molecules of around 350-400 amino acids in length, defined by a characteristic pattern of conserved cysteine residues, along with other invariant amino acids (see <http://www.stanford.edu/~rnusse/wntwindow.html>).

20

In the 1970s, the *wingless* (*wg*¹) mutation of *Drosophila melanogaster* was described, in which affected individuals showed aberrant wing and haltere development (Sharma, 1973; Sharma and Chopra, 1976). When the gene disrupted by this mutation was subsequently identified, the predicted 468aa peptide sequence exhibited remarkable similarity to that of a murine gene, *int-1* (Cabrera et al., 1987; Rijsewijk et al., 1987), including an identical pattern of 23 conserved cysteine residues. *int-1* had earlier been identified as a common integration site of the murine mammary tumour virus, and a likely cellular oncogene (Nusse and Varmus, 1982; van Ooyen and Nusse, 1984). Thus, the two prototypic members of the *Wnt* gene family were described. Since that time, numerous homologues of *wingless/int-1* have

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been identified in divergent organisms, including *Caenorhabditis elegans*, *Drosophila melanogaster*, *Xenopus laevis*, chicken, mouse and humans (reviewed in Cadigan and Nusse, 1997; Wodarz and Nusse, 1998). Lower organisms appear to possess a limited repertoire of *Wnt* genes in comparison to higher organisms, presumably reflecting their lesser developmental complexity. Additionally, vertebrates appear to express multiple, closely related orthologues of certain *Wnts*. The *Wnt* family is composed of more than 60 members, with 14 human homologues alone. Well-documented roles exist for *Wnt* signalling in a variety of developmental processes, including cell fate specification and patterning within the central nervous system.

Wnt ligands interact with membrane-bound receptors of the frizzled family, leading to activation of a cytoplasmic protein, Dishevelled. Dishevelled inhibits Notch activation (2) and also inhibits the activity of an Axin-APC-GSK-3 β complex, promoting formation of a bipartite transcriptional activator comprising b-catenin and TCF (4). Wnt signalling may be antagonised by extracellular molecules that compete for Wnt binding, including frizzled related proteins (FRP), Wnt inhibitory factors (WIF), Dickkopf and Cerberus. Expression of *Wnt* target genes may also be regulated by other proteins that bind to and alter the function of TCF. CREB-Binding Protein (CBP) exhibits a mutually antagonistic binding affinity for TCF with b-catenin and converts TCF into a repressor of target genes (8). Additionally, Notch activation may induce transcriptional repression by TCF, even in the presence of b-catenin, through expression of the TLE class of putative target genes (5,7).

As a model system to test the involvement of *Notch* and *Wnt* genes in the differentiation of ES cells we have used embryonal carcinoma cells which are stem cells of teratocarcinomas. The stem cells of early embryos and the stem cells of teratocarcinomas have been demonstrated experimentally to be capable of substituting for one another in their respective roles. Thus, an embryonic stem cell introduced to a syngeneic host may give rise to a teratocarcinoma containing all of the elements that would be found in a spontaneous tumour of this type (Mintz et al

1978). Likewise, embryonal carcinoma cells derived from a spontaneous germ cell carcinoma may participate in embryonic development, and generate normal somatic tissue following injection into a blastocyst (Brinster 1974; Mintz and Illmensee 1975; Papaioannou et al 1975). This clearly demonstrates that murine EC cells may respond
5 to developmental cues in an appropriate manner, and that their differentiation may provide information pertinent to normal embryogenesis. Similarly, human EC cells may provide an insight into the processes that regulate human development.

The TERA2 cell line was derived from a lung metastasis of a human teratocarcinoma
10 in the mid 1970s (Fogh and Trempe, 1975). Morphologically, TERA2 cultures are quite divergent from the characteristic EC phenotype and display significant heterogeneity, suggesting that these cells undergo spontaneous differentiation (Andrews et al., 1980). However, a tumour containing both embryonal carcinoma cells and differentiated derivatives was produced following injection of TERA2 into
15 a nude mouse host (Andrews et al., 1983a; Andrews et al., 1983b; Andrews et al., 1984). A cell line established from the EC component of this tumour, named NTERA2, closely resembled and maintained the characteristic EC phenotype in culture and, unlike the parent line, was able to produce teratocarcinoma in nude mice with high frequency (Andrews et al., 1983a; Andrews et al., 1983b; Andrews et al.,
20 1984). Additionally, various subclones of NTERA2 exhibit the ability to differentiate extensively *in vitro* following treatment with chemical inducers (eg retinoic acid (RA), HMBA) (Andrews, 1984; Andrews et al., 1986).

The expression of human *Notch* homologues were examined in NTERA2 to
25 determine their involvement in ES cell differentiation.

We have discovered that members of the *Notch* gene family, *Notch1* (Genbank accession number AF308602), *Notch2* (Genbank accession number NM_024408) and *Notch3* (Genbank accession number NM_000435) are expressed in EC cells and
30 NTERA2 cells. *Notch1* expression was detected as a mRNA band of around 7Kb in both EC and differentiated cultures of NTERA2. *Notch3*, like *Notch1*, was

examined in EC cells. A transcript of around 8Kb was readily detected in all samples. The endoderm-specific *Notch4* (Genbank accession number XM_004207) was not.

5 All three *Notch* homologues expressed by NTERA2 showed altered transcription during differentiation in response to retinoic acid. In each case, however, these changes were modest and expression was evident in both EC and differentiated cultures. The role of the Notch pathway in directing EC/ES differentiation may thus depend to a greater extent on the level of signalling activation rather than the abundance of the receptors. In order to investigate this possibility, the expression of
10 candidate ligands for Notch receptors were examined. For example, *dlk* (Genbank accession number U15979) was detected at high levels in EC cultures, but its expression was almost extinguished by 3 days following RA treatment. Low levels were also observed through 7 and 14 days post-RA. However, by 21 days, *dlk* was up-regulated to the level seen in EC cultures. These profound changes may reflect an
15 important role for *dlk* and other DSL ligands in regulating EC/ES differentiation through altered Notch signalling activation. This data is suggestive that the *Notch* signalling pathway is involved in regulating EC cell differentiation and, by extrapolation, human ES cell differentiation.

20 A degenerate PCR strategy was used to investigate the possible expression of novel *Wnt* genes in the NTERA2 system. The expression of a single *Wnt* gene, *Wnt-13*, was detected in NTERA2. *Wnt-13* was absent in EC cells, but showed induction and subsequent up-regulation following both retinoic acid and HMBA treatment. Both of these agents bring about extensive differentiation of NTERA2, accompanied by the
25 loss of typical human EC surface markers.

We have examined the expression of components of the *Wnt* pathway and of transcripts corresponding to other proteins known to interact with *Wnt* signalling in NTERA2 cells. These cells are a model system for aspects of human embryogenesis
30 and differentiate extensively *in vitro* in response to chemical inducers. Among the

cell types produced following retinoic acid treatment are functional, post-mitotic, CNS neurons (1,6,17).

5 The modulation of the *Notch* and *Wnt* signalling pathways may facilitate manipulation of embryonic stem cell differentiation. The term modulation refers to either the maintenance of embryonic stem cells as embryonic stem cells or the facilitation of differentiation of embryonic stem cells along defined cell lineages.

10 According to an aspect of the invention there is provided a method to modulate the phenotype of an embryonic stem cell comprising contacting said cell with a ligand binding domain of a polypeptide wherein said domain binds its cognate receptor expressed by said cell to modulate said phenotype.

15 According to a further aspect of the invention there is provided a method to modulate the differentiation of an embryonic stem cell comprising:

- i) providing a culture of embryonic stem cells;
- ii) providing at least one ligand, or the active binding fragment thereof, capable of binding its cognate receptor polypeptide expressed by said embryonic stem cell;
- 20 iii) forming a culture comprising embryonic stem cells and said ligand; and
- iv) growing said cell culture.

In a preferred method of the invention said ligand is encoded by a nucleic acid molecule selected from the group consisting of:

- 25 i) a nucleic acid molecule as represented in Figure 22;
- ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of binding a Wnt receptor; and
- iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

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In a preferred method of the invention said ligand is selected from the group consisting of: WNT 1; WNT 2, WNT 3; WNT 4; WNT 5A; WNT 6; WNT 7A; WNT 8B; WNT 10B; WNT 11; WNT 14; WNT 16.

5 In a further preferred method of the invention said ligand is WNT 13.

In an alternative preferred method of the invention said ligand is encoded by a nucleic acid molecule selected from the group consisting of:

- 10 i) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, or 18.
- ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and
- 15 iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

In a further preferred method of the invention said ligand is selected from the group represented by the amino acid sequences in Figures 3, 6, 8, 9, 11, 13, 15, 17, 19, or polypeptide variants thereof.

20 Polypeptide variants are polypeptide sequences having at least 75% identity with the polypeptide sequences as herein disclosed, or fragments and functionally equivalent polypeptides thereof. In one embodiment, the polypeptides have at least 85% identity, more preferably at least 90% identity, even more preferably at least 95% identity, still
25 more preferably at least 97% identity, and most preferably at least 99% identity with the amino acid sequences illustrated herein.

In a further preferred method of the invention said cells are induced to differentiate by the addition of at least one agent selected from the group consisting of: retinoic
30 acid; HMBA ; bone morphogenetic proteins ; bromodeoxyuridine; lithium; sonic hedgehog .

Optionally the inducing agent and the ligand are added simultaneously to a culture of embryonic stem cells. Alternatively, the ligand is added before addition of said inducing agent.

- 5 According to a further aspect of the invention there is provided a method for modulating the differentiation of embryonic stem cells comprising:
- i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
 - a) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, 18.
 - 10 b) a nucleic acid molecule which hybridises to the nucleic acid in (ii) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and
 - c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
 - ii) forming a culture comprising the cell identified in (i) above with an
15 embryonic stem cell; and
 - iii) growing said culture under conditions suitable for the maintenance and/or differentiation of said embryonic stem cell.

- According to a yet further aspect of the invention there is provided a method for
20 modulating the differentiation of embryonic stem cells comprising:
- i) providing a cell transfected with a nucleic acid molecule selected from the group comprising:
 - a) a nucleic acid molecule as represented by the sequence in Figure 22;
 - b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and
25 which encodes a ligand capable of binding a Wnt receptor; and
 - c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
 - ii) forming a culture comprising a cell as identified in (i) above with an embryonic stem cell; and
 - 30 iii) growing said culture under conditions suitable for the maintenance and/or differentiation of embryonic stem cells.

In a preferred method of the invention said cell expresses Wnt-13.

5 Optionally the cells expressing the ligand(s) are mixed with a culture of undifferentiated embryonic stem cells. This is followed by addition of the inducing agent (eg retinoic acid; HMBA, bone morphogenetic proteins; bromodeoxyuridine; lithium; sonic hedgehog).

10 In a preferred method of the invention said nucleic acid molecule hybridises under stringent hybridisation conditions to the nucleic acid molecules represented in (a), (b) or (c) above.

Stringent hybridisation or washing conditions are well known in the art. For example, nucleic acid hybrids that are stable after washing in 0.1xSSC, 0.1% SDS at 60°C. It is
15 well known in the art that optimal hybridisation conditions can be calculated if the sequence of the nucleic acid is known. For example, hybridisation conditions can be determined by the GC content of the nucleic acid subject to hybridisation. Please see Sambrook *et al* (1989) Molecular Cloning; A Laboratory Approach. A common formula for calculating the stringency conditions required to achieve hybridisation
20 between nucleic acid molecules of a specified homology is:

$$T_m = 81.5^{\circ} \text{C} + 16.6 \text{ Log } [\text{Na}^+] + 0.41 [\% \text{ G} + \text{C}] - 0.63 (\% \text{ formamide})$$

25 In a further preferred method of the invention the nucleic acid molecule is genomic DNA or cDNA.

In a preferred method of the invention the nucleic acid molecule encodes a ligand of human origin.
30

In a further preferred method of the invention said embryonic stem cells are of human origin.

In a yet further preferred method of the invention the cell transfected with the nucleic acid according to the invention is a mammalian cell. Preferably the cell is selected from the following group: a chinese hamster ovary cell; murine primary fibroblast cell; human primary fibroblast cell; transformed mouse fibroblast cell-line STO.

According to a further aspect of the invention there is provided a method for inhibiting the differentiation of embryonic stem cells or embryonal carcinoma cells comprising:

10

- i) providing at least one polypeptide, or active fragment thereof, wherein said polypeptide is an inhibitor of the *Wnt* signalling pathway.
- ii) forming a culture comprising the polypeptide identified in (i) above with an embryonic stem cell; and
- 15 iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

In a preferred method of the invention said inhibitor of Wnt signalling is selected from the group comprising the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); 20 Dickkopf; Cerebrus.

In a further preferred method of the invention said inhibitor of Wnt signalling is selected from the group comprising the active binding fragments thereof of the following polypeptides: SFRP1; SFRP4; FRZB; SFRP2; FZD1; FZD2; FZD9; FZD3; 25 FZD5; FZD4; FZD6; FZD7; DVL2; DVL3; GSK3B; AXIN1; APC; TCF1; WIF-1; CER 1; DKK1-4; SARP 2; SARP 3.

According to a further aspect of the invention there is provided a method for inhibiting the differentiation of embryonic stem cells or embryonal carcinoma cells comprising:

30

- i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
 - a) a nucleic acid molecule encoding a Wnt inhibitory polypeptide;
 - 5 b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and which encodes a polypeptide capable of inhibiting *Wnt* signalling; and
 - c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
- ii) contacting the cell of (i) above with a culture of embryonic stem cells; and
- 10 iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

In a preferred method of the invention said cells express at least one Wnt inhibitory polypeptide selected from the group comprising the active binding fragments thereof

15 of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus. Preferably said cells express at least one Wnt inhibitory polypeptide selected from the group comprising the active binding fragments thereof of the following polypeptides: SFRP1; SFRP4; FRZB; SFRP2; FZD1; FZD2; FZD9; FZD3; FZD5; FZD4; FZD6; FZD7; DVL2; DVL3; GSK3B;

20 AXIN1; APC; TCF1; WIF-1; CER-1; DKK1-4

In a further preferred method of the invention the nucleic acid molecule is encoded by a nucleic acid molecule which hybridises under stringent hybridisation conditions to the nucleic acid molecules represented in (a), (b) or (c) above. Preferably said

25 inhibitors are human.

According to a further aspect of the invention there is provided a vector comprising the nucleic acid molecule according to the invention. Preferably the vector is an expression vector adapted for the expression of the polypeptide encoded by said

30 nucleic acid molecule.

Typically said adaptation includes, by example and not by way of limitation, the provision of transcription control sequences (promoter sequences) which mediate cell/tissue specific expression. These promoter sequences may be cell/tissue specific, inducible or constitutive.

5

- Promoter is an art recognised term and, for the sake of clarity, includes the following features which are provided by example only, and not by way of limitation. Enhancer elements are *cis* acting nucleic acid sequences often found 5' to the transcription initiation site of a gene (enhancers can also be found 3' to a gene sequence or even located in intronic sequences and is therefore position independent). Enhancers function to increase the rate of transcription of the gene to which the enhancer is linked. Enhancer activity is responsive to *trans* acting transcription factors (polypeptides) which have been shown to bind specifically to enhancer elements. The binding/activity of transcription factors (please see Eukaryotic Transcription Factors, by David S Latchman, Academic Press Ltd, San Diego) is responsive to a number of environmental cues which include, by example and not by way of limitation, intermediary metabolites (eg glucose, lipids), environmental effectors (eg light, heat,).
- Promoter elements also include so called TATA box and RNA polymerase initiation selection (RIS) sequences which function to select a site of transcription initiation. These sequences also bind polypeptides which function, *inter alia*, to facilitate transcription initiation selection by RNA polymerase.
- Adaptations also include the provision of selectable markers and autonomous replication sequences which both facilitate the maintenance of said vector in either the eukaryotic cell or prokaryotic host. Vectors which are maintained autonomously are referred to as episomal vectors. Episomal vectors are desirable since these molecules can incorporate large DNA fragments (30-50kb DNA). Episomal vectors of this type are described in WO98/07876. Alternatively, the vector is an integrating vector.

Adaptations which facilitate the expression of vector encoded genes include the provision of transcription termination/polyadenylation sequences. This also includes the provision of internal ribosome entry sites (IRES) which function to maximise expression of vector encoded genes arranged in bicistronic or multi-cistronic expression cassettes.

These adaptations are well known in the art. There is a significant amount of published literature with respect to expression vector construction and recombinant DNA techniques in general. Please see, Sambrook et al (1989) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbour Laboratory, Cold Spring Harbour, NY and references therein; Marston, F (1987) *DNA Cloning Techniques: A Practical Approach Vol III* IRL Press, Oxford UK; DNA Cloning: F M Ausubel et al, *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc.(1994).

Conventional methods to introduce DNA or vector DNA into cells are well known in the art and typically involve the use of chemical reagents, cationic lipids or physical methods. Chemical methods which facilitate the uptake of DNA by cells include the use of DEAE –Dextran (Vaheri and Pagano *Science* 175: p434) . DEAE-dextran is a negatively charged cation which associates and introduces the DNA into cells but which can result in loss of cell viability. Calcium phosphate is also a commonly used chemical agent which when co-precipitated with DNA introduces the DNA into cells (Graham et al *Virology* (1973) 52: p456).

The use of cationic lipids (eg liposomes, Felgner (1987) *Proc.Natl.Acad.Sci USA*, 84:p7413) has become a common method since it does not have the degree of toxicity shown by the above described chemical methods. The cationic head of the lipid associates with the negatively charged nucleic acid backbone of the DNA to be introduced. The lipid/DNA complex associates with the cell membrane and fuses with the cell to introduce the associated DNA into the cell. Liposome mediated DNA transfer has several advantages over existing methods. For example, cells which are

recalcitrant to traditional chemical methods are more easily transfected using liposome mediated transfer.

5 More recently still, physical methods to introduce DNA have become effective means to reproducibly transfect cells. Direct microinjection is one such method which can deliver DNA directly to the nucleus of a cell (Capecchi (1980) *Cell*, 22:p479). This allows the analysis of single cell transfectants. So called "biolistic" methods physically shoot DNA into cells and/or organelles using a particle gun (Neumann (1982) *EMBO J*, 1: p841). Electroporation is arguably the most popular method to
10 transfect DNA. The method involves the use of a high voltage electrical charge to momentarily permeabilise cell membranes making them permeable to macromolecular complexes. However physical methods to introduce DNA do result in considerable loss of cell viability due to intracellular damage. These methods therefore require extensive optimisation and also require expensive equipment.

15

More recently still a method termed immunoporation has become a recognised technique for the introduction of nucleic acid into cells, see Bildirici et al, *Nature* 405, 769. The technique involves the use of beads coated with an antibody to a specific receptor. The transfection mixture includes nucleic acid, typically vector
20 DNA, antibody coated beads and cells expressing a specific cell surface receptor. The coated beads bind the cell surface receptor and when a shear force is applied to the cells the beads are stripped from the cell surface. During bead removal a transient hole is created through which nucleic acid and/or other biological molecules, eg polypeptides, can enter. Transfection efficiency of between 40-50% is achievable
25 depending on the nucleic acid used.

Other non-liposome based, chemical transfectant agents have become available, for example ExGen500 (polyethylenimine), produced by MBI Fermentas. ExGen500 is particularly effective for transfection of human ES cells (Eiges, 2001).

30

According to a further aspect of the invention there is provided a method for the production of the polypeptide encoded by the nucleic acid molecule according to the invention comprising:

- 5 i) providing a cell transformed/transfected with a nucleic acid molecule according to the invention;
- ii) growing said cell in conditions conducive to the manufacture of said polypeptide; and
- i) purifying said polypeptide from said cell, or its growth environment.

10 In a preferred method of the invention said nucleic acid molecule is the vector according to the invention.

In a further preferred method of the invention said vector encodes, and thus said recombinant polypeptide is provided with, a secretion signal to facilitate purification of said polypeptide.

15

According to a further aspect of the invention there are provided host cells which have been transformed/transfected with the vector according to the invention, so as to include at least part of the polypeptide according to the invention, so as to permit expression of at least the functional part of the polypeptide encoded by said nucleic acid molecule.

20

Ideally said host cells are eukaryotic cells, for example, insect cells such as cells from a species *Spodoptera frugiperda* using the baculovirus expression system.

25 According to a further aspect of the invention there is provided a therapeutic cell composition comprising differentiated or differentiating embryonic stem cells derived by the method according to the invention. Preferably said composition is for

use in the treatment of: Parkinson's disease; Huntington's disease; motor neurone disease; heart disease; diabetes; liver disease (eg cirrhosis); renal disease; AIDS.

5 According to a further aspect of the invention there is provided a method of treatment of an animal comprising administering a cell composition comprising embryonic stem cells which have been induced to differentiate into at least one cell-type.

10 According to a yet further aspect of the invention there is provided condition medium obtained by culturing embryonic stem cells according to any of the methods hereindisclosed.

An embodiment of the invention will now be described by example only and with reference to the following figures:

15 Figure 1 is a schematic representation of conserved domains in Notch polypeptides;

Figure 2 is the nucleic acid sequence of murine notch ligand delta-like 1;

20 Figure 3 is the amino acid sequence of murine notch ligand delta-like 1;

Figure 4 is the nucleic acid sequence of murine notch ligand jagged 1;

25 Figure 5 is the nucleic acid sequence of human notch ligand jagged 1 (alagille syndrome) (JAG1);

Figure 6 is the amino acid sequence of human notch ligand jagged 1 (alagille syndrome);

30 Figure 7 is the nucleic acid sequence of human notch ligand jagged 2 (JAG2)

Figure 8 is the amino acid sequence of human notch ligand jagged 2 (JAG2);

Figure 9 is the amino acid sequence of murine notch ligand jagged 1;

Figure 10 is the nucleic acid sequence of murine notch ligand jagged 2;

5

Figure 11 is the amino acid sequence of murine notch ligand jagged 2;

Figure 12 is the nucleic acid sequence of human notch ligand delta-like 3 (DLL3);

10 Figure 13 is the amino acid sequence of human notch ligand delta-like 3 precursor polypeptide;

Figure 14 is the nucleic acid sequence of human notch ligand delta-1 (DLL1);

15 Figure 15 is the amino acid sequence of murine notch ligand delta-like 1;

Figure 16 is the nucleic acid sequence of human notch ligand delta-like 4 (DLL4);

Figure 17 is the amino acid sequence of human notch ligand delta-like 4 (DLL4);

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Figure 18 is the nucleic acid sequence of murine notch ligand delta-like 4(DLL4);

Figure 19 is the amino acid sequence of murine notch ligand delta-like 4(DLL4);

25 Figure 20 is a western blot of cell extracts of various EC cell-lines probed with Notch 2 antisera;

Figure 21 represents northern blot analysis of the expression patterns of notch genes (*Notch 1,2,3*) and notch ligands (*Dlk, jagged 1*) in EC cells and EC cells treated with retinoic acid (RA);

30

Figure 22 represents the nucleic acid sequence of human *Wnt 13*;

Figure 23 is a diagrammatic representation of the Wnt signalling pathway;

- 5 Figure 24 represents northern blot analysis of *Wnt 13* and mRNA's corresponding to Frizzled receptors and Frizzled related protein antagonists of Wnt signalling in NTERA 2 cells various Wnt inhibitors after exposure of NTERA 2 cells;

10 Figure 25 represents a northern blot analysis of intracellular components of Wnt signalling pathway in NTERA 2 cells;

Figure 26 represents the nucleic acid sequence of human *dickkopf1*;

15 Figure 27 represents the nucleic acid sequence of human *dickkopf2*;

Figure 28 represents the nucleic acid sequence of human *dickkopf3*; and

Figure 29 represents the nucleic acid sequence of human *dickkopf4*;

20 Figure 30 represents the nucleic acid sequence of WNT-1;

Figure 31 represents the amino acid sequence of WNT-1;

25 Figure 32 represents the nucleic acid sequence of WNT-2;

Figure 33 represents the amino acid sequence of WNT-2;

Figure 34 represents the nucleic acid sequence of WNT 2B;

30 Figure 35 represents the amino acid sequence of WNT 2B;

Figure 36 represents the nucleic acid sequence of WNT 3;

Figure 37 represents the amino acid sequence of WNT 3;

5 Figure 38 represents the nucleic acid sequence of WNT 4;

Figure 39 represents the amino acid sequence of WNT 4;

10 Figure 40 represents the nucleic acid sequence of WNT 5A;

Figure 41 represents the amino acid sequence of WNT 5A;

Figure 42 represents the nucleic acid sequence of WNT 6;

15 Figure 43 represents the amino acid sequence of WNT 6;

Figure 44 represents the nucleic acid sequence of WNT 7A;

20 Figure 45 represents the amino acid sequence of WNT 7A;

Figure 46 represents the amino acid sequence of WNT 7B;

Figure 47 represents the nucleic acid sequence of WNT 8B;

25 Figure 48 represents the amino acid sequence of WNT 8B;

Figure 49 represents the nucleic acid sequence of WNT 10B;

30 Figure 50 represents the amino acid sequence of WNT 10B;

Figure 51 represents the nucleic acid sequence of WNT 11;

Figure 52 represents the amino acid sequence of WNT 11;

Figure 53 represents the nucleic acid sequence of WNT 14

5

Figure 54 represents the amino acid sequence of WNT 14;

Figure 55 represents the nucleic acid sequence of WNT 16;

10 Figure 56 represents the amino acid sequence of WNT 16;

Figure 57 represents the nucleic acid sequence of FZD 1;

Figure 58 represents the amino acid sequence of FZD 1;

15

Figure 59 represents the nucleic acid sequence of FZD 2;

Figure 60 represents the amino acid sequence of FZD 2;

20 Figure 61 represents the nucleic acid sequence of FZE 3;

Figure 62 represents the amino acid sequence of FZE 3;

Figure 63 represents the nucleic acid sequence of FZD 4;

25

Figure 64 represents the amino acid sequence of FZD 4;

Figure 65 represents the nucleic acid sequence of FZD 5;

30 Figure 66 represents the amino acid sequence of FZD 5;

Figure 67 represents the nucleic acid sequence of FZD 6;

Figure 68 represents the amino acid sequence of FZD 6;

5 Figure 69 represents the nucleic acid sequence of FZD 7;

Figure 70 represents the amino acid sequence of FZD 7;

Figure 71 represents the nucleic acid sequence of FZD 8;

10

Figure 72 represents the amino acid sequence of FZD 8;

Figure 73 represents the nucleic acid sequence of FZD 9;

15 Figure 74 represents the amino acid sequence of FZD 9;

Figure 75 represents the nucleic acid sequence of FZD 10;

Figure 76 represents the amino acid sequence of FZD 10;

20

Figure 77 represents the nucleic acid sequence of FRP;

Figure 78 represents the amino acid sequence of FRP;

25 Figure 79 represents the nucleic acid sequence of SARP 1;

Figure 80 represents the amino acid sequence of SARP 1;

Figure 81 represents the nucleic acid sequence of SARP 2;

30 Figure 82 represents the amino acid sequence of SARP 2;

Figure 83 represents the nucleic acid sequence of FRZB;

Figure 84 represents the amino acid sequence of FRZB;

5 Figure 85 represents the nucleic acid sequence of FRPHE;

Figure 86 represents the amino acid sequence of FRPHE;

Figure 87 represents the nucleic acid sequence of SARP 3;

10

Figure 88 represents the amino acid sequence of SARP 3;

Figure 89 represents the nucleic acid sequence of CER 1;

15 Figure 90 represents the amino acid sequence of CER 1;

Figure 91 represents the nucleic acid sequence of DKK1;

Figure 92 represents the amino acid sequence of DKK1;

20

Figure 93 represents the nucleic acid sequence of DKK 2;

Figure 94 represents the amino acid sequence of DKK 2;

25 Figure 95 represents the nucleic acid sequence of DKK 3;

Figure 96 represents the amino acid sequence of DKK 3;

Figure 97 represents the nucleic acid sequence of DKK 4;

30 Figure 98 represents the amino acid sequence of DKK 4;

Figure 99 represents the nucleic acid sequence of WIF-1;

Figure 100 represents the amino acid sequence of WIF-1;

5 Figure 101 represents the nucleic acid sequence of SRFP 1;

Figure 102 represents the amino acid sequence of SRFP 1;

Figure 103 represents the nucleic acid sequence of SRFP 4;

10

Figure 104 represents the amino acid sequence of SRFP 4; and

Figure 105 represents a diagram depicting the pCMV-tracer vector.

15 **Materials and Methods**

Table 1 Cell lines derived from germ cell tumours.

Cell Line	Biopsy Site	Biopsy Histology	Xenograph	Reference
Histology				
2102Ep	Testis	EC, T, Y	EC	(Andrews <i>et al.</i> , 1980)
833KE	Testis	EC, T, C, S	EC	(Andrews <i>et al.</i> , 1980)
TERA-1	Lung	EC, T		(Fogh and Trempe, 1975)
NTERA2 cl. D1	Lung	EC, T	EC, T	(Fogh and Trempe, 1975) (Andrews, 1984)

Abbreviations used: EC, embryonal carcinoma, T, teratoma, S, seminoma, C, choriocarcinoma, Y, yolk-sac carcinoma

Cell Lines derived from gestational choriocarcinomas.

BEWO	Corresponds to gestational choriocarcinoma	(Pattillo and Gay, 1968)
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5 List of Antibodies Used

Antibody	Reference	References
SSEA-3	Andrews et. al., 1982	12
SSEA-4	Kannagi et. al., 1983	18
Tra-1-60	Andrews et. al., 1984	25
Tra-1-81	Andrews et. al., 1984	25
Tra-2-54	Andrews et. al., 1984	20
Tra-2-49	Andrews et. al., 1984	20
A2B5	Fenderson et. al., 1987	
ME311	Fenderson et. al., 1987	
Vin-is-56	Andrews et. al., 1990	44
Vin-is-53	Andrews et. al., 1990	44
Vin-2PB-22	Andrews et. al., 1990	44
Thy-1	Andrews et. al., 1983	10

Expression Vectors

- 10 The following mammalian expression vectors are used in the expression of ligands hereindisclosed:

Purchased from Stratagene Inc. pExchange-1; pExchange-2; pExchange-3A, 3B, 3C; pExchange-4A, 4B, 4C; pExchange-5A, 5b, 5C; pExchange-6A, 6B, 6C; pExchange module EC-hyg; pExchange module EC-Puro; pExchange module EC-Neo; pCMV-Script; pCMV-Tag1; pCMV-Tag2; pCMV-Tag3; pCMV-Tag4; pCMV-Tag5; 15 pCMVLACI, pOPRSVI/MCS, pOPI3-CAT ; pERV3; pEGSH.

Purchased from Invitrogen Inv.**T-REX System vectors**

- 20 pcDNA4/TO; pcDNA4/TO/myc-His; pcDNA6/TR; pT-Rex-DEST30; pT-Rex-DEST31; pcDNA4/TO-E; pcDNA5/FRT/TO; pcDNA5/FRT/TO-TOPO.

Geneswitch System vectors

pGene/V5-His A, B, C; pSwitch

5 **Ecdysone-Inducible System**

PVgRXR; pIND; pIND(SP1); pIND/V5-His; pIND/V5-His-TOPO; pIND/GFP;
pIND(SP1)/GFP.

10 **PShooter vectors**

pRF/Myc/Nuc; pCMV/Myc/nuc; pEF/myc/mito; pCMV/myc/mito; pEF/myc/ER;
pCMV/myc/ER; pEF/myc/cyto; pCMV/myc/cyto.

15 **INVITROGEN INC**

pTet-off; pTet-on; pTA-2/ /3 /4; pTet-tTS; pTRE2hyg
PTRE2pur; pTRE2; pLP-TRE2; PTRE-Myc; pTRE-HA; pTRE-6xHN
pTRE-d2EGFP; pBI; pBI-EGFP; pBI-G; pBI-L; pTK-Hyg

20

“Living colours” vectors.

pDsRed2-N1; pDsRed2-C1; pECFP-N1; pEGFP-N1; pEGFP-N2; pEGFP-N3
pEYFP-N1; pECFP-C1; pEGFP-C1; pEGFP-C2; pEGFP-C3
25 pEYFP-C1; pd1EGFP-N1; pd1ECFP-N1; pd2EGFP-N1; pd2EYFP-N1
pd4EGFP-N1; pCMS-EGFP; pHygEGFP; pEGFPLuc; pNF- κ B-dsEGFP
pIRES2-EGFP; pIRES-EYFP

Maintenance of cell lines

30

All cells were grown in Dulbecco's modified Eagle's medium (DMEM),
supplemented with 10% by volume foetal calf serum (Gibco BRL) and 2mM L-
glutamine. Tissue culture flasks were incubated in a humidified atmosphere of 10%
CO₂ in air at 37°C.

35

Treatment of NTERA2 Cells

Retinoic acid

- 5 Medium was aspirated from confluent flasks of EC cells and the cells rinsed in sterile PBS. 1ml of 0.25% (w/v) trypsin in 2mM EDTA was added per 75cm² flask and the flask incubated at room temperature for up to 5 minutes. Vigorous shaking was subsequently used to dislodge the cells. Cells were suspended in 9ml of supplemented DMEM per ml of trypsin used and counted in a haemocytometer. Cells
- 10 were seeded at 10⁶ cells per 75cm² flask, in medium containing 10⁻⁵M all-*trans*-retinoic acid (Eastman Kodak), diluted from a 10⁻²M stock solution in dimethyl sulfoxide (DMSO). Flasks were incubated as described above and the media replaced as and when required.

15 Hexamethylene bisacetamide (HMBA)

Cells to be treated with HMBA were prepared as described for retinoic acid, but grown in medium supplemented with 10⁻³M HMBA instead of RA.

Harvesting of cells

- 20 Cells were dislodged from the culture vessel with trypsin and suspended in 9ml culture medium per ml of trypsin solution used, as described above. The cell suspension was then centrifuged at 400 x g for 3 minutes and the medium aspirated from the resulting cell pellet. Cells were then rinsed in 5ml PBS and centrifuged again at 400 x g for 1 minute. The PBS rinse was aspirated and the cells stored at –
- 25 80°C or used immediately.

Total RNA preparation

- Where possible, all vessels and all solutions used in RNA preparation and storage
- 30 were treated with a 0.01% (v/v) solution of diethylpyrocarbonate (DEPC) in distilled water, and subsequently autoclaved.

TRI reagent (Sigma) was added to pelleted cells in a quantity corresponding to 1ml per 75cm² flask. The lysate was agitated until homogenous. 0.2ml of chloroform was added per ml of TRI reagent used and the vessel vortexed for 10 seconds. After 10 minutes at room temperature, the lysate was centrifuged at 12000 x g for 15 minutes at 4°C. Following centrifugation, the aqueous (uppermost) phase was transferred to a fresh vessel and 0.5ml of isopropanol added per ml of TRI reagent used. The sample was incubated at room temperature for 10 minutes, then centrifuged at 12000 x g for 10 minutes at 4°C. Following centrifugation, the supernatant was removed and the pellet washed in 70% ethanol. RNA was dissolved in DEPC-treated, double-distilled water.

Isolation of mRNA

100mg oligo dT cellulose (Ambion) was suspended in 25ml binding buffer. Up to 2mg of total RNA was then added to the binding buffer and the suspension gently agitated at room temperature for 45 minutes. The suspension was then centrifuged at 3000 x g for 10 minutes and the supernatant discarded. The resulting pellet was re-suspended in a further 25ml of binding buffer and agitated at room temperature for 60 minutes. The suspension was again centrifuged at 3000 x g and the supernatant discarded. The pellet of oligo dT cellulose was transferred to a spin column using a minimal quantity of binding buffer to re-suspend. The column was spun at maximum speed in a desktop microfuge for 30 seconds and the eluate discarded. This was repeated until the cellulose was dry. 200µl of wash buffer was then added to the cellulose and mixed in with a pipette tip. The column was spun at maximum speed for 1 minute and the eluate discarded. 200µl of DEPC-treated, double-distilled H₂O was then added to the cellulose and mixed in, as before. The column was then spun at maximum speed for 2 minutes and the eluted mRNA collected.

Precipitation of RNA

To the RNA solution was added 0.1x volume of 5M LiCl and 2.5x volume of 100% ethanol. After vortexing briefly, the sample was incubated at -20°C for >60 minutes

to precipitate. Precipitated RNA was centrifuged at maximum speed in a bench top microfuge for 30 minutes. The supernatant was discarded and the pellet rinsed in 70% ethanol, then dissolved in H₂O.

Quantitation of nucleic acid

5

A Beckman DU 650 spectrophotometer was used for the quantitation of both DNA and RNA. The machine was set to measure absorbance at wavelengths of 260nm and 280nm. After blanking the machine on an appropriate solution, diluted DNA or RNA samples in a volume of 100µl were added to the cuvette and measured. The
10 absorbance at 260nm was used to calculate nucleic acid concentration in µg/µl, as shown below:

$$[\text{Nucleic acid}] = (A^{260} \times N \times \text{DF}) \div 1000$$

15 Where N is 33 for single-stranded DNA, 50 for double-stranded DNA and 40 for RNA and DF is the dilution factor for the sample added to the cuvette.

Northern blot analysis

Blot preparation

20 1g of agarose was dissolved in 85ml H₂O by boiling. After cooling to around 70°C, 10ml of 10x MOPS buffer and 5ml of formaldehyde were added, and the gel cast. 1-5µg of each mRNA sample was mixed with an appropriate quantity of 10x RNA loading buffer to give a final volume of no more than 30µl. The RNA was then denatured at 95°C for 2 minutes and quenched on ice for 10 minutes. The gel was
25 placed in an electrophoresis tank containing 1x MOPS buffer and the samples loaded into each well of the gel, along with appropriate molecular weight markers in the outermost wells. 80V were applied across the gel for 2-3 hours or as required. Following electrophoresis, the outermost lanes containing the molecular weight markers were removed using a scalpel and submerged in double-distilled H₂O
30 containing ethidium bromide at 0.5µg/ml. The remainder of the gel was submerged in >5 volumes of double-distilled H₂O, which was replaced every 5 minutes for a total

of 25 minutes. An appropriately sized piece of GeneScreen Plus (DuPont) membrane, just larger than the area of gel to be blotted, was cut. The membrane was hydrated by briefly submerging in double-distilled H₂O, then transferred to 10x SSC, concurrent with the last 15 minutes of gel washing. The blotting apparatus was assembled as shown in Figure 2.1, with the gel upside-down, using 10x SSC transfer buffer. After transfer of at least 6 hours, the absorbent material was removed from the membrane. After marking the position of the wells using a pencil, the membrane was removed from the gel and washed briefly in 2x SSC. Whilst still damp, the RNA was fixed to the membrane by UV crosslinking. The membrane was then baked at 80°C for 3 hours.

The excised marker lanes were de-stained by soaking in a large volume of double-distilled H₂O for around 3 hours, after which they were visualised on a UV transilluminator and photographed.

15

Probe preparation

Random-primed DNA labelling was carried out using the Prime-a-Gene kit from Promega. Approximately 25ng of template DNA (PCR or restriction digest product) was denatured at 95°C for 2 minutes, then quenched on ice for 10 minutes. The reaction mix was then assembled on ice, in the order indicated below:

10µl of 5x labelling buffer
H₂O to give a final volume of 50µl
2µl unlabelled dNTP mix (0.5mM each)
25ng of denatured/quenched template DNA
2µl 10mg/ml BSA
5µl αP³²dATP 3000Ci/mmol (NEN DuPont)
1µl DNA polymerase 1 large (Klenow) fragment

30

The labelling reaction mix was incubated at room temperature for 2 hours. After this period, unincorporated nucleotides were removed using Pharmacia S-300 MicroSpin columns. Columns were placed in a microfuge tube and pre-spun at 735 x g for 1 minute. The column was then transferred to a fresh tube and the entire labelling
 5 reaction added. The column was then spun at 735 x g for a further 2 minutes and the purified, labelled DNA collected. Labelled DNA was denatured at 95°C for 2 minutes, then quenched on ice for 15 minutes.

Hybridisation and washing procedure

10 Northern blots were equilibrated in 150ml of 2x SSC at 42°C for 15 minutes in a hybridisation oven at 8 RPM. The SSC was exchanged for 25ml of hybridisation buffer, pre-warmed to 42°C, and the filter incubated for a further 30 minutes at the same temperature. The entire volume of purified probe solution was then added to
 15 the hybridisation buffer and the blot incubated overnight at 42°C/ 8 RPM. The hybridisation solution was then discarded and the blot washed as follows:

2x SSC at room temperature for 20 minutes
 2x SSC at room temperature for 20 minutes
 20 2x SSC/1% SDS at 65°C for 45 minutes
 2x SSC/1% SDS at 65°C for 45 minutes
 0.1x SSC at room temperature for 20 minutes
 0.1x SSC at room temperature for 20 minutes
 25 Filters were exposed to a Bio Rad BI phosphor-imager screen overnight and, in most cases, subsequently exposed to X-ray film (Kodak X-omat AR).

Loading controls for Northern blots

30 All Northern blots used in this study were probed with β -actin as a loading control. Table 2.5 (overleaf) lists the figures to which each control probing (panel A to T, Figure 2.2) corresponds. Northern blot data presented in this study have not, in all

cases, been subject to repeat experiments using RNA isolated from different batches of cells. These data may not be regarded as conclusive, since reproducibility has not been proven.

5 **Method for Analysis of the Requirement for Notch Ligands in the Differentiation of Embryonic Stem, Embryonal Carcinoma and their Differentiated Derivatives.**

CHO are transfected with constructs encoding either membrane bound or soluble
10 forms of the Notch ligands. These cell lines are used to support the growth of either Embryonal carcinoma cells (EC) e.g NTERA2/cl.D1 or Human embryonic stem cells (hES).

The transfected CHO cells (CHO(DSL)) are used in the following way. To assess
15 membrane bound forms of the Notch ligands the CHO(DSL) cells are used as feeder cells (i.e. the EC or hES will be grown on top of the CHO(DSL) cells). To assess the soluble forms of the Notch ligands either supernatant from the transfected CHO cells or concentrated ligand molecules derived from the supernatant are added to the culture medium of the EC and hES cells.

20

Notch Ligand Constructs.

The following cloned Notch ligands were obtained from Dr. Shigeru Chiba, Department of Hematology, Oncology and Cell Therapy, Transplantation Medicine.
25 Graduate School of Medicine. University of Tokyo.

Delta1-FLAG

Jagged1-FLAG

Jagged2-FLAG

30

Soluble Delta1-Fc

Soluble Jagged1-Fc

Soluble Jagged2-Fc

These had been cloned into the vector pTRACER-CMV from Invitrogen, Fig 30).

- 5 The clones used consisted either of the full length ligand linked to a histidine tag (FLAG, Kodak Inc.), or a ligand lacking the membrane spanning and intracellular portion of the protein thus rendering the ligand soluble. These had been linked to the Fc portion of human IgG.

10 **Generation of Notch Ligand expressing Cell lines**

- The Chinese Hamster Ovary derived cell line AA8 was maintained in MEM Alpha medium with Glutamax-1 supplemented with ribonucleosides and deoxyribonucleosides (Lifetechnologies) and 10% Foetal Bovine Serum
15 (FBS)(Lifetechnologies).

Plasmid was transfected into the AA8 cells using either Fugene (Roche) or Lipofectin (Lifetechnologies) or Superfect (Qiagen) according to manufacturers protocols.

20 **Assessment of Transiently Transfected Cell lines for Ligand Production.**

Both soluble and membrane bound forms of the Notch ligand's production are assayed by western blotting and chemiluminescent detection.

- 25 Cells transfected with the ligand encoding constructs are harvested and the proteins extracted. Due to the tagging of the ligands proteins are able to be run out on an SDS-PAGE gel, blotted and probed with either mouse anti-FLAG antibody and detected using a anti-mouse HRP secondary or an HRP-secondary antibody. Both methods use electro-chemiluminescence (ECL) as the detection method.

30

Concentration of Soluble Notch ligand from the Supernatant of Transfected CHO cells.

- 5 Fc-labelled Notch ligand can be purified from transfected CHO cells supernatant using a HiTrap protein G HP column (Amersham Pharmacia Biotech). A sample can be analysed by western blotting as described above.

Embryonic Cell culture.

- 10 Human Embryonal Carcinoma NTERA2/D1 cells are maintained in Dulbecco's modified Eagles medium (DMEM), supplemented with 2mM l-glutamine, 10% Foetal Bovine Serum (Lifetechnologies) and at 37°C under 10% CO₂ in air. Cells were passaged by scraping from the surface of the tissue culture flask with 3mm glass beads and reseeded at 5 x 10⁶ cells per 75cm³ flask. For specific seeding densities
15 cells were pasaaged using 0.25% Trypsin (Lifetechnologies) in Dulbecco's Phosphate Buffered Saline (PBS) supplemented with 1mM EDTA.

- Human Embryonic Stem Cells are maintained on irradiated mouse embryonic fibroblasts in serum free conditions, with 80% F12:DMEM (Lifetechnologies), 20%
20 Knockout SR (Lifetechnologies), 1% Non-essential amino acid solution (Lifetechnologies), 1 mM L-glutamine, 0.1mM β-mercaptoetanol (Sigma) 4 ng/ml bFGF (Sigma). The cells are passaged using collagenase IV and scraping.

Flow Cytofluorimetry

- 25 Cells were removed from their adherent culture surface and incubated with suitable primary antibody for 1 hour at 4C. Cells are washed in PBS with 5% FCS and incubated for a further hour with a suitable FITC-conjugated labelled secondary antibody, and analysed on a EPICS Elite ESP Flow Cytometer (Coulter Electronics). Colonies were assessed for the presence of embryonal stem cell markers such as
30 SSEA-3, -4, Tra-1-60 and for appearance of markers of differentiated marker antigens such as A2B5, ME311 and N901.

Design of oligonucleotide primers

Primers for use in PCR were designed on a Macintosh Power PC, using the "Primer Select" program of the DNASTAR software package (DNASTAR Inc.). All primers
5 used in this study are shown in Table 2

Table 2 List of oligonucleotide primers

Gene	GenBank accession	Primer direction	Primer location	Primer sequence 5' to 3'
<i>Wnt-13</i>	Z71621	Forward	1159-1178	Tgagtgggtcctgtactctg
		Reverse	1503-1484	Actcacactgggtaacacgg
<i>SFRP4</i>	XM_004706	Forward	858-880	Agaggagtggctgcaatgaggtc
		Reverse	1159-1142	Gcgcccggtgttttctt
<i>Waf1</i>	U03106	Forward	487-506	Cagggctgaaaacggcggca
		Reverse	947-928	Aggagccacaccctccaga
β -actin	NM_001101	Forward	326-357	Atctggcaccacaccttacaatgagctgc g
		Reverse	1163-1132	Cgtcactactcctgcttgctgatccacatctgc
<i>neuroD1</i>	NM_002500	Forward	240-263	Aagccatgaacgcagaggaggact
		Reverse	818-799	Agctgtccatggtaccgtaa

All PCR data presented in this study were duplicated in independent experiments to
10 eliminate the possibility of methodological error. However, duplicate experiments
were performed on identical samples and do not, therefore, control for variability
between separate batches of cells. Polymerase chain reactions from which
quantitative interpretations were to be made were controlled by parallel amplification
of the cyclin-dependent kinase inhibitor, *Waf1*. This transcript has been demonstrated
15 by other workers in the laboratory to be constitutively expressed by NTERA2 EC
cells and differentiated derivatives (unpublished data). Furthermore, *Waf1* has been
shown to exhibit an approximately 20-fold lower abundance in the NTERA2 system
than the more widely used control, β -actin, and is therefore well suited to the analysis
of rare transcripts.

20

PCR Reaction conditions

PCR mixes were assembled on ice, with the following components per reaction:

- 5
10
15
- 5µl of 25mM MgCl₂
 - 5µl of 10x reaction buffer
 - 5µl of 1mM dNTPs
 - 3µl of forward primer at 5pmol/µl
 - 3µl of reverse primer at 5pmol/µl
 - 0.3µl of Taq polymerase at 1 unit/µl (Promega)
 - template and H₂O to give 50µl final volume

10 A premix was made containing all reaction components bar the template. Premix was then added to the reaction vessels containing the template, on ice. The reaction vessels were then transferred to the thermal cycler. The PCR programs used are shown in Table 3, with cycling from T1→T2→T3→T1.

Table 3 PCR thermal cycling programs

15

	Program 1	Program 2	Program 3	Program 4
T1 (temp/duration)	96°C/30 seconds	94°C/60 seconds	94°C/90 seconds	95°C/90 seconds
T2 (temp/duration)	50°C/15 seconds	55°C/90 seconds	60°C/90 seconds	63°C/60 seconds
T3 (temp/duration)	60°C/240 seconds	72°C/60 seconds	72°C/120 seconds	72°C/60 seconds
Cycles	25	35	35	35

List of DNA and protein accession numbers of genes used in results

20

Gene Name	Description	cDNA Accession Number	Protein Accession Number
WNT2B	wingless-type MMTV integration site family, member 2B	AB045116	Q93097

	member 2B		
SFRP1	secreted frizzled-related protein 1	AF056087	AAC12877
SFRP4	secreted frizzled-related protein 4	AF026692	AAC04617
FRZB	frizzled-related protein	NM_001463	NP_001454
SFRP2	secreted frizzled-related protein 2		
FZD1	frizzled (Drosophila) homolog 1	AB017363	BAA34666
FZD2	frizzled (Drosophila) homolog 2	NM_001466	NP_001457
FZD9	frizzled (Drosophila) homolog 9	HSU82169	AAC51174
FZD3	frizzled (Drosophila) homolog 3	Kirikoshi et. al., 2000	Kirikoshi et. al., 2000
FZD5	frizzled (Drosophila) homolog 5		
FZD4	frizzled (Drosophila) homolog 4	NM_012193	NP_036325
FZD6	frizzled (Drosophila) homolog 6	AB012911	BAA25686
FZD7	frizzled (Drosophila) homolog 7	AB017365	BAA34668
DVL2	dishevelled 2 (homologous to Drosophila dsh)	NM_004422	NP_004413
DVL3	dishevelled 3 (homologous to Drosophila dsh)	NM_004423	NP_004414
GSK3B	glycogen synthase kinase 3 beta	NM_002093	NP_002084
AXIN1	axin	AF009674	AAC51624
APC	adenomatosis polyposis coli	NM_000038	NP_000029
TCF1	transcription factor 1, hepatic; LF-B1, hepatic nuclear factor (HNF1), albumin proximal factor	M57732	AAA88077

Examples

Expression of a single Wnt gene, Wnt-13(2B) was detected. This transcript was absent in NTERA2 EC cells, but showed marked up-regulation following RA treatment, figure 24. Members of the FRP family, encoding putative Wnt antagonists,

5

also showed altered expression during differentiation, figure 24. Both Frp-1 and SARP-1 were down-regulated following RA treatment, whilst FrpHE was absent in EC cells, but expressed at high levels in RA treated cultures.

- 5 Several members of the frizzled family were also detected, providing a candidate receptor system for Wnt-13, figure 24. Two of these, hFz-4 and hFz-6, showed developmental regulation. Transcripts corresponding to intracellular components of the Wnt pathway, including Dishevelled, GSK-3b, Axin, APC and TCF were present at equivalent levels in EC and differentiating cultures. CBP was also ubiquitously
10 expressed.

15

REFERENCES

1. Andrews P.W. and Roberts D.B. (1974) The preparation and characterization of chromatin from third instar larvae of *Drosophila melanogaster*. *Nucleic Acids Res.* 1: 979-997.
- 20 2. Roberts D.B. and Andrews P.W. (1975) *Drosophila* chromatin: An immunological study. *Nucleic Acids Res.* 2:1291-1303.
3. Andrews P.W. and Boyse E.A. (1978) Mapping of an H-2-linked gene that influences mating preference in mice. *Immunogenetics* 6:265-268.
4. Yamazaki K., Yamaguchi M., Andrews P.W., Peake B. and Boyse E.A. (1978)
25 Mating preferences in F₂ segregants of crosses between MHC-congenic mouse strains. *Immunogenetics* 6: 253-259.
5. Andrews P.W. and Wachtel S.S. (1979) Rejection of C57BL skin grafts by (C57BL x *Mus musculus castaneus*) F₁ hybrids. *Transplantation* 27: 43-44.
6. Andrews P.W. and Goodfellow P.N. (1980) Antigen expression by somatic cell
30 hybrids of a murine embryonal carcinoma cell with thymocytes and L cells. *Somat. Cell Genet.* 6: 271-284.

7. Bronson D.L., Andrews P.W., Solter D., Cervenka J., Lange P.H. and Fraley E.E. (1980) A cell line derived from a metastasis of a human testicular germ-cell tumor. *Cancer Res.* 40: 2500 - 2506.
8. *Andrews P.W., Bronson D.L., Benham F., Strickland S. and Knowles B.B. (1980)
5 A comparative study of eight cell lines derived from human testicular teratocarcinoma. *Int. J. Cancer* 26: 269-280.
9. Andrews P.W., Knowles B.B. and Goodfellow P.N. (1981) A human cell surface antigen defined by a monoclonal antibody and controlled by a gene on chromosome 12. *Somat. Cell Genet.* 7: 435-443.
- 10 10. Andrews P.W., Bronson D.L., Wiles M.V. and Goodfellow P.N. (1981) The expression of major histocompatibility antigens by human teratocarcinoma derived cells lines. *Tissue Antigens* 17: 493-500.
11. Benham F.J., Andrews P.W., Bronson D.L., Knowles B.B. and Harris H. (1981)
15 Alkaline phosphatase isozymes as possible markers of differentiation in human teratocarcinoma cell lines. *Dev. Biol.* 88: 279-287.
- 12 Andrews P.W., Goodfellow P.N., Shevinsky L., Bronson D. L. and Knowles B.B. (1982) Cell surface antigens of a clonal human embryonal carcinoma cell line: Morphological and antigenic differentiation in culture. *Int. J. Cancer* 29: 523-531.
13. Andrews P.W. (1982) Human embryonal carcinoma cells in culture do not
20 synthesize fibronectin until they differentiate. *Int. J. Cancer* 30: 567-571.
14. Damjanov I. and Andrews P.W. (1983) Ultrastructural differentiation of a clonal human embryonal carcinoma cell line *in vitro*. *Cancer Res.* 43: 2190-2198.
15. Matthaei K., Andrews P.W. and Bronson D.L. (1983) Retinoic acid fails to induce differentiation in human teratocarcinoma cell lines that express high levels of
25 cellular receptor protein. *Exp. Cell Res.* 143: 471-474.
16. Cossu G., Andrews P.W. and Warren L. (1983) Covalent binding of lactosaminoglycans and heparan sulphate to fibronectin synthesized by a human teratocarcinoma cell line. *Biochem. Biophys. Res. Comm.* 111: 952-957.
17. Tunnacliffe A., Goodfellow P.N., Banting G., Solomon E., Knowles B.B. and
30 Andrews P.W. (1983) Human chromosome 11 carries at least 4 genes controlling expression of cell surface antigens. *Somat. Cell Genet.* 9: 629-642.

18. Kannagi R., Cochran N.A., Ishigami F., Hakomori S.-i., Andrews P.W., Knowles B.B. and Solter D. (1983a) Stage-specific embryonic antigens (SSEA-3 and -4) are epitopes of a unique globo-series ganglioside isolated from human teratocarcinoma cells. *The EMBO J.* 2: 2355-2361.
- 5 19. *Andrews P.W., Damjanov I., Simon D., Banting G., Carlin C., Dracopoli N.C. and Fogh J. (1984b) Pluripotent embryonal carcinoma clones derived from the human teratocarcinoma cell line Tera-2: Differentiation *in vivo* and *in vitro*. *Lab. Invest.* 50: 147-162.
- 10 20. Andrews P.W., Meyer L.J., Bednarz K.L. and Harris H. (1984c) Two monoclonal antibodies recognizing determinants on human embryonal carcinoma cells react specifically with the liver isozyme of human alkaline phosphatase. *Hybridoma* 3: 33-39.
- 15 21. *Gönczöl E., Andrews P.W. and Plotkin S.A. (1984) Cytomegalovirus replicates in differentiated but not undifferentiated human embryonal carcinoma cells. *Science* 224: 159-161.
22. *Andrews P.W. (1984) Retinoic acid induces neuronal differentiation of a cloned human embryonal carcinoma cell line *in vitro*. *Dev. Biol.* 103: 285-293.
23. Oosterhuis J.W., Andrews P.W., Knowles B.B. and Damjanov I. (1984) Effects of cisplatin on embryonal carcinoma cell lines *in vitro*. *Int. J. Cancer* 34: 133-139.
- 20 24. Blaineau C., Connan F., Arnaud D., Andrews P.W., Williams L., McIlhinney R.A.J. and Avner P. (1984) Definition of three species-specific monoclonal antibodies recognizing antigenic structures present on human EC cells which undergo modulation during *in vitro* differentiation. *Int. J. Cancer* 34: 487-494.
- 25 25. Andrews P.W., Banting G.S., Damjanov I., Arnaud D. and Avner P. (1984a) Three monoclonal antibodies defining distinct differentiation antigens associated with different high molecular weight polypeptides on the surface of human embryonal carcinoma cells. *Hybridoma* 3: 347-361.
26. Damjanov I., Clark C.K. and Andrews P.W. (1984) Cytoskeleton of human embryonal carcinoma cells. *Cell Differentiation* 15: 133-139.
- 30 27. Andrews P.W., Knowles B.B., Parkar M., Pym B., Stanley K. and Goodfellow P.N. (1985) A human cell-surface antigen defined by a monoclonal antibody and controlled by a gene on human chromosome 1. *Ann. Human Genet.* 49: 31-39.

28. Gönczöl E., Andrews P.W. and Plotkin S.A. (1985) The replication of human cytomegalovirus in human teratocarcinoma cell lines. *J. Gen. Virol.* 66: 509-515.
29. Damjanov I., Damjanov A. and Andrews P.W. (1985) Trophoblastic carcinoma: Mouse teratocarcinoma-derived tumor stem cells differentiating into trophoblastic and yolk sac elements. *J. Embryol. Exp. Morph.* 86: 125-141.
30. Carlin C.R. and Andrews P.W. (1985) Human embryonal carcinoma cells express low levels of functional receptor for epidermal growth factor. *Exp. Cell. Res.* 159: 17-26.
31. Andrews P.W., Damjanov I., Simon D. and Dignazio M. (1985) A pluripotent human stem cell clone isolated from the TERA-2 teratocarcinoma line lacks antigens SSEA-3 and SSEA-4 *in vitro* but expresses these antigens when grown as a xenograft tumor. *Differentiation* 29: 127-135.
32. Lee V.M-Y. and Andrews P.W. (1986) Differentiation of NTERA-2 clonal human embryonal carcinoma cells into neurons involves the induction of all three neurofilament proteins. *J. Neurosci.* 6: 514-521.
33. Andrews P.W., Gönczöl E., Plotkin S.A., Dignazio M. and Oosterhuis J.W. (1986) Differentiation of TERA-2 human embryonal carcinoma cells into neurons and HCMV permissive cells: Induction by agents other than retinoic acid. *Differentiation* 31: 119-126.
34. Tippet P., Andrews P.W., Knowles B.B. Solter D. and Goodfellow P.N. (1986) Red cell antigens P (globoside) and Luke: Identification by monoclonal antibodies defining the murine stage-specific embryonic antigens -3 and -4 (SSEA-3 and -4). *Vox Sang.* 51: 53-56.
35. Swallow D.M., Povey S., Parkar M., Andrews P.W., Harris H., Pym B. and Goodfellow P.N. (1986) Mapping of the gene coding for the human liver/bone/kidney isozyme of alkaline phosphatase to chromosome 1. *Ann. Human Genet.* 50: 229-235.
36. Andrews P.W., Trinchieri G., Perussia B. and Baglioni C. (1987) Induction of class 1 major histocompatibility complex antigens in human teratocarcinoma cells by interferon without induction of differentiation, growth inhibition or resistance to viral infection. *Cancer Res.* 47: 740-746.

37. *Fenderson B.A., Andrews P.W., Nudelman E., Clausen H. and Hakomori S.-i. (1987) Glycolipid core structure switching from globo- to lacto- and ganglio-series during retinoic acid-induced differentiation of TERA-2-derived human embryonal carcinoma cells. *Dev. Biol.* 122: 21-34.
- 5 38. Zhang X.-Y., Loflin P.T., Gehrke C.W., Andrews P.W. and Ehrlich M. (1987) Hypermethylation of human DNA sequences in embryonal carcinoma cells and somatic tissues but not in sperm. *Nucleic Acids Res.* 15: 9429-9449.
39. Mavilio F., Simeone A., Boncinelli E. and Andrews P.W. (1988) Activation of four homeobox gene clusters in human embryonal carcinoma cells induced to
10 differentiate by retinoic acid. *Differentiation* 37: 73-79.
40. Williams B.P., Daniels G.L., Pym B., Sheer D., Povey S., Okubo Y., Andrews P.W. and Goodfellow P.N. (1988) Biochemical and genetic analysis of the OKa blood group antigen. *Immunogenetics* 27: 322-329.
41. Rendt J., Erulkar S. and Andrews P.W. (1989) Presumptive neurons derived by
15 differentiation of a human embryonal carcinoma cell line exhibit tetrodotoxin-sensitive sodium currents and the capacity for regenerative responses. *Exp. Cell Res.* 180: 580-584.
42. Chen C., Fenderson B.A., Andrews P.W. and Hakomori S.-i. (1989) Glycolipid-glycosyltransferases in human embryonal carcinoma cells during retinoic acid-
20 induced differentiation. *Biochemistry* 28: 2229-2238.
43. Andrews P.W., Gönczöl E., Fenderson B.A., Holmes E.H., O'Malley G., Hakomori S. -i and Plotkin S.A. (1989). Human cytomegalovirus induces stage-specific embryonic antigen-1 in differentiating human teratocarcinoma cells and fibroblasts. *J. Exp. Med.* 169: 1347-1359.
- 25 44. Andrews P.A., Nudelman E., Hakomori S. -i. and Fenderson B.A. (1990). Different patterns of glycolipid antigens are expressed following differentiation of TERA-2 human embryonal carcinoma cells induced by retinoic acid, hexamethylene bisacetamide (HMBA) or bromodeoxyuridine (BUdR). *Differentiation* 43: 131-138.
45. *Simeone A., Acampora D., Arcioni L., Andrews P.W., Boncinelli E. and Mavilio
30 F. (1990). Sequential activation of human HOX2 homeobox genes by retinoic acid in human embryonal carcinoma cells. *Nature* 346: 763-766.

46. Hirka G., Prakesh K., Kawashima H., Plotkin S.A., Andrews P.W. and Gönczöl E. (1991). Differentiation of human embryonal carcinoma cells induces human immunodeficiency virus permissiveness which is stimulated by human cytomegalovirus coinfection. *J. Virol.* 65: 2732-2735.
- 5 47. Marrink J., Andrews P.W., van Brummen P.J., de Jong H.J., Sleijfer D., Schraffordt-Koops H. and Oosterhuis J.W. (1991). TRA-1-60: A new serum marker in patients with germ cell tumors. *Int. J. Cancer* 49: 368-372.
48. Zeichner S.L., Hirka G., Andrews P.W. and Alwine J.C. (1992). Differentiation-dependent HIV LTR regulatory elements active in human teratocarcinoma cells. *J. Virol.* 66: 2268-2273.
- 10 49. Fenderson B.A., Radin N. and Andrews P.W. (1993) Differentiation antigens of human germ cell tumors: distribution of carbohydrate epitopes on glycolipids and glycoproteins analysed using PDMP, an inhibitor of glycolipid synthesis. *European Urology.* 23: 30-37.
- 15 50. Giwereman, A., Andrews, P.W., Jørgensen, N., Muller, J., Graem, N., Skakkebaek, N.E. (1993) Immunochemical expression of embryonal marker TRA-1-60 in carcinoma in situ germ cells and in testicular germ cell tumours. *Cancer*, 72: 1308-1314.
- 20 51. Rideg K., Hirka G., Prakash K., Bushar L., Nothias, J-Y, Weinmann R., Andrews P.W. and Gönczöl E. (1994) DNA binding proteins that interact with the 19-base pair (CRE-like) element from the HCMV immediate early promoter in differentiating human embryonal carcinoma cells. *Differentiation*, 56: 119-129.
- 25 52. Wenk, J., Andrews, P.W., Casper, J., Hata, J-I., Pera, M.F., von Keitz, A., Damjanov, I., Fenderson, B.A. 1994. Glycolipids of germ cell tumours: extended globo-series glycolipids are a hallmark of human embryonal carcinoma cells. *Int. J. Cancer.* 58: 108-115.
53. Ackerman S.L., Knowles B.B., Andrews P.W. (1994). Gene regulation during neuronal and non-neuronal differentiation of NTERA2 human teratocarcinoma-derived stem cells. *Mol. Brain Res.* 25: 157-162.
- 30 54. *Andrews P.W., Damjanov I., Berends J., Kumpf S., Zappavingna V. Mavilio F. and Sampath K. (1994). Inhibition of proliferation and induction of differentiation

- of pluripotent human embryonal carcinoma cells by osteogenic protein-1 (or bone morphogenetic protein-7). *Laboratory Investigation* 71: 243-251.
55. Damjanov, I., Zhu, Z.M., Andrews, P.W., Fenderson, B.A. (1994). Embryonal carcinoma cells differentiate into parietal endoderm via an intermediate stage corresponding to primitive endoderm. *In Vivo* 8: 967-974.
 56. Squires, P.E., Wakeman, J.A., Chapman, H., Kumpf, S., Fiddock, M.D., Andrews, P.W. and Dunne, M.J. (1996). Regulation of intracellular Ca^{2+} in response to muscarinic and glutamate receptor agonists during the differentiation of NTERA2 human embryonal carcinoma cells into neurons. *European Journal of Neuroscience* 8: 783-793.
 57. Andrews, P.W., Casper, J., Damjanov, I., Duggan-Keen, M., Giwerzman, A., Hata, J.I., von Keitz, A., Looijenga, L.H.J., Millán, J.L., Oosterhuis, J.W., Pera, M., Sawada, M., Schmoll, H.J., Skakkaebæk, N.E., van Putten, W. and Stern, P. (1996). Comparative analysis of cell surface antigens expressed by cell lines derived from human germ cell tumours. *Int. J. Cancer* 66: 806-816.
 58. Gels, M.E., Marrink J, Visser, P., Sleijfer, D.T., Droste J.H.J., Hoekstra, H.J., Andrews, P.W., Koops, H.S. (1997). Importance of a new tumour marker TRA-1-60 in the follow-up of patients with clinical stage I nonseminomatous testicular germ cell tumours. *Annals of Surgical Oncology* 4: 321-327.
 59. Wakeman, J.A., Heath, P.R., Pearson, R.C.A., Andrews, P.W. (1997) MAL mRNA is induced during the differentiation of human embryonal carcinoma cells into neurons, and is also localised within specific regions of the human brain. *Differentiation* 62:97-105.
 60. *Wakeman, J.A., Walsh, J., Andrews, P.W., (1998). Human Wnt-13 is developmentally regulated during the differentiation of NTERA-2 pluripotent human embryonal carcinoma cells. *Oncogene* 17:179-186
 61. Giesberts, A.N., Duran, C., Morton, I.E., Piggot, C., White, S.J., Andrews, P.W. (1999). The expression and function of cadherin-mediated cell-to-cell adhesion in human embryonal carcinoma cells. *Mechanisms of Development* 83 115-125.
 62. *Badcock, G., Pigott, C., Goepel, J., Andrews, P.W. (1999). The Human Embryonal Carcinoma Marker Antigen TRA-1-60 Is A Sialylated Keratan Sulphate Proteoglycan.

Cancer Research 59 4715-4719.

- 5 63. Gokhale, P.J., Giesberts, A.N., Andrews, P.W. (2000). *Brachyury* is Expressed by Human Teratocarcinoma Cells in the Absence of Mesodermal Differentiation. *Cell Growth and Differentiation* 11 157-162.
- 64 *Przyborski, S.A., Morton, I.E., Wood, A., Andrews, P.W. (2000) Developmental Regulation of Neurogenesis in the Pluripotent Human Embryonal Carcinoma Cell Line NTERA-2. *Eur. J. Neurosci.* 12: 3521 - 3528.
- 10
65. Andrews P.W. and Knowles B.B. (1982) Human teratocarcinoma: Tools for human embryology In: *Teratocarcinoma and Embryonic Cell Interactions* (T. Murumatsu, G. Gachelin, A.A. Moscona, and Y. Ikawa, eds). Japan Scientific Societies Press, Tokyo, pp 19-30.
- 15
- 66 Andrews P.W., Knowles B.B., Cossu G. and Solter D. (1982) Teratocarcinoma and mouse embryo cell surface antigens: Characterization of the molecule(s) carrying the SSEA-1 antigenic determinant. In: *Teratocarcinoma and embryonic Cell Interactions* (T. Murumatsu, G. Gachelin, A.A. Moscona and Y. Ikawa eds). Japan Scientific Societies Press, Tokyo, pp 103-119.
- 20
- 67 Goodfellow P.N. and Andrews P.W. (1982) Sexual differentiation and H-Y antigen(s). *Nature, News and Views* 295: 11-13.
68. Andrews P.W. and Goodfellow P.N. (1982) Analysing the mouse T/t complex. *Nature, News and Views* 299: 296-297.
- 25 69. Goodfellow P.N. and Andrews P.W. (1982) The biology of teratocarcinomas. (Meeting Report). *Nature, News and Views* 300: 107-108.
70. Andrews P.W. (1983) The characteristics of cell lines derived from human germ cell tumors. In: *The Human Teratomas: Experimental and Clinical Biology* (I. Damjanov, B.B. Knowles and D. Solter eds). Humana Press, Clifton, NJ, pp 285-311.
- 30 71. Benham F.J., Wiles, M.V., Banting G., Andrews P.W. and Goodfellow P.N. (1983) Human-mouse teratocarcinoma hybrids: A tool for analysis of gene activity in early

- human development. In: Human Teratomas: Experimental and Clinical Biology (I. Damjanov, B.B. Knowles and D. Solter, eds.). Humana Press, Clifton, NJ, pp 313-314.
72. Andrews P.W., Goodfellow P.N. and Damjanov I. (1983) Human teratocarcinoma cells in culture. *Cancer Surveys* 2: 41-73.
- 5 73. Goodfellow P.N. and Andrews P.W. (1983) Is there a human T/t locus? *Nature, News and Views* 302: 657-658.
74. Andrews P.W., Goodfellow P.N. and Bronson D.L. (1983) Cell surface characteristics and other markers of differentiation of human teratocarcinomas in culture. In: Teratocarcinoma Stem Cells. Cold Spring Harbor Conferences on Cell Proliferation, 10 Vol. 10 (L.M. Silver, G.R. Martin and S. Strickland, eds.) pp 579-590.
- 10 75. Goodfellow P.N., Benham F., Andrews P.W., Trowsdale J., Lee J. and Quintero M. (1983) Developmental genetics of MHC expression using human-mouse hybrid cell lines. In: Teratocarcinoma Stem Cells. Cold Spring Harbor Conferences on Cell Proliferation, Vol. 10 (L.M. Silver, G.R. Martin and S. Strickland, eds.), pp 439-449.
- 15 76. Bronson D.L., Andrews P.W., Vessella R.L. and Fraley E.E. (1983) *In vitro* differentiation of human embryonal carcinoma cells. In: Teratocarcinoma Stem Cells. Cold Spring Harbor Conferences on Cell Proliferation, Vol. 10 (L.M. Silver, G.R. Martin and S. Strickland, eds.), pp 597-605.
77. Andrews P.W. (1984) The male specific antigen (H-Y) and sexual differentiation. In: 20 Genetic Analysis of the Cell Surface (P.N. Goodfellow, ed.). Chapman and Hall, London, pp 159-190.
78. Andrews P.W. and Damjanov I. (1985) Immunocytochemistry of human teratocarcinoma stem cells. In: Monoclonal Antibodies in Cancer (S. Sell and R.A. Reisfeld, eds.). The Humana Press Inc., Clifton, NJ, pp 339-364.
- 25 79. Andrews P.W. (1985) Properties of cloned human embryonal carcinoma cells and their differentiation *in vitro*. In: Germ Cell Tumors II: Proceedings of the 2nd Germ Cell Tumor Conference, Leeds (W.G. Jones, A. Milford-Ward and C.K. Anderson, eds.). Pergamon Press, Oxford, pp 71-75.
80. Damjanov I., Clark R.K. and Andrews P.W. (1985) Expression of keratin polypeptides 30 in human embryonal carcinoma cells. *Ann. NY Acad. Sci.* 455: 732-733.

- 5 81. Oosterhuis J.W., Andrews P.W. and de Jong, B. (1986) Mechanisms of therapy related differentiation in testicular germ cell tumors. In: Biochemical Mechanisms of the Platinum Anti-tumor Drugs (D.C.H. McBrien and T.F. Slater, eds.). Proceedings of an Association for International Cancer Research Symposium. IRL Press, Oxford, pp 65-90.
82. Andrews, P.W., Oosterhuis J.W. and Damjanov I. (1987) Cell lines from human germ cell lines. In: Teratocarcinomas and embryonic stem cells: A practical approach (E.J. Robertson, ed.). IRL Press, Oxford, pp 207-248.
- 10 83. Andrews P.W., Fenderson B.A. and Hakomori S.-i. (1987) Human embryonal carcinoma cells and their differentiation in culture. *Int. J. Androl.* 10: 95-104.
84. Andrews P.W. (1987) Human teratocarcinoma stem cells: Glycolipid antigen expression and modulation during differentiation. *J. Cell Biochem.* 35: 321-332.
- 15 85. Andrews P.W. (1988) The properties of human teratocarcinoma *in vitro*. In *In Vitro Models for Cancer Research* (M. Webber and L. Sekely, eds.). CRC Press, Boca Raton, FL, pp 191-213.
86. Andrews P.W. (1988) Induction of differentiation in neoplastic cells. Editorial commentary. In *Oncology Overview: Selected Abstracts on Induction of Differentiation in Neoplastic Cells*. CIDA-CCB Information Ventures, Inc., Philadelphia, PA.
87. Andrews P.W. (1988) Human teratocarcinoma. *Biochim. Biophys. Acta* 948: 17-36.
- 20 88. Andrews P.W. and Oliver R.T.D. (1990) (Editors) Germ Cell Tumours of the Testis: Cancer Surveys 9 [Editorial Commentary, pp 239-241].
89. Andrews P.W., Marrink J., Hirka G., von Keitz A., Sleijfer D. and Gönczöl E. (1991) The surface antigen phenotype of human embryonal carcinoma cells: Modulation upon differentiation and viral infection. In: *Recent Results in Cancer Research, Vol 123; Pathobiology of Human Germ Cell Neoplasia* (J.W. Oosterhuis, H. Walt and I. Damjanov, eds.). Springer-Verlag, pp 63-83.
- 25 90. Bottero L., Simeone A., Arcioni L., Acampora D., Andrews P.W., Boncinelli E. and Mavilio F. (1991) Differential activation of homeobox genes by retinoic acid in human embryonal carcinoma cells. In: *Recent Results in Cancer Research, Vol 123; Pathobiology of Human Germ Cell Neoplasia* (J.W. Oosterhuis, H. Walt and I. Damjanov, eds.). Springer-Verlag, pp 133-143.
- 30

91. McCarrick J. and Andrews P.W. (1992) Embryonal carcinoma cells and embryonic stem cells as models for neuronal development and function. In: Cell Lines in Neurobiology: A Practical Approach (J. Wood, ed.). IRC Press, Oxford pp 77-104.
- 5 92. Fenderson B.A. and Andrews P.W. (1992) Carbohydrate antigens of embryonal carcinoma cells; changes upon differentiation. Acta Path. Microbiol. Immunol. Scand. Vol. 100, Suppl. 27 "Carbohydrate Pathology". (Dabelsteen, E. & Clausen, H., eds), Munksgaard Copenhagen, pp 109-118.
- 10 93. Andrews, P.W. (1993). Teratomas - the cross roads of embryology and oncology. Oncology Newsletter (Journal of the Yorkshire Regional Cancer Organisation), No. 14 pp 16-17.
94. Andrews P.W., Damjanov I. (1994) Cell lines from human germ cell tumors. In: Atlas of Human Tumor Cell Lines (R.J. Hay, J-G Park, A. Gazdar, eds.). Academic Press, pp 443-476.
- 15 95. Oosterhuis, J.W., Andrews, P.W. (1996). Differentiation in germ cell tumours. In: Testicular Cancer (2nd Edition) (A. Horwich, ed) Chapman & Hall, pp 61-72.
96. Andrews, P.W., Wakeman, J. (1996). Cell differentiation in germ cell tumours. In: "Ares Sero Conference on Sex Differentiation" (I.A. Hughes, ed), Frontiers in Endocrinology vol. 20, pp 33-44
- 20 97. Andrews, P.W., (1998) Teratocarcinomas and human embryology: pluripotent human EC cell lines. Acta Pathologica Microbiologica et Immunologica Scandinavica, 106:158-168.
- 25 98. Gokhale, P.J., Eastwood, D., Walsh, J., Andrews, P.W. (1998). The possible role of Notch genes in Germ Cell Tumour Development and Progression. Germ Cell Tumours IV (W G Jones, I Appleyard, P Handen & J K Joffe, eds), John Libby, London, pp 69-71.
99. Andrews, P.W. (2001) Life story inside a cell. Times Higher Education Supplement. Jan 19th 2001, p21.
- 30 100. Andrews, P.W., Przyborski, S.A. and Thomson, J.A. (2000). Embryonal Carcinoma Cells as Embryonic Stem Cells. Cold Spring Harbor Laboratory Press. In press.

CLAIMS

1. A method to modulate the differentiation of an embryonic stem cell
5 comprising:

- i) providing a culture of embryonic stem cells;
- ii) providing at least one ligand, or the active binding fragment thereof, capable of binding its cognate receptor polypeptide expressed by said embryonic stem cell;
- 10 iii) forming a culture comprising embryonic stem cells and said ligand; and
- iv) growing said cell culture.

2. A method according to Claim 1 wherein said ligand is encoded by a nucleic acid molecule selected from the group consisting of:

- 15 i) a nucleic acid molecule as represented in Figure 22;
- ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of binding a Wnt receptor; and
- iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

20

3. A method according to Claim 2 wherein said ligand is encoded by a nucleic acid molecule selected from the nucleic acid sequences represented in: Fig 30; Fig 32; Fig 34; Fig 36; Fig 38; Fig 40; Fig 42; Fig 44; Fig 47; Fig 49; Fig 51; Fig 53; Fig 55.

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4. A method according to Claim 2 or 3 wherein said ligand is encoded by a nucleic acid molecule as represented by the nucleic acid sequence in Fig 22.

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5. A method according to Claim 1 wherein said ligand is encoded by a nucleic acid molecule selected from the group consisting of:
- i) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, or 18.
 - 5 ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and
 - iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.
- 10 6. A method according to Claim 5 wherein said ligand is selected from the group comprising the amino acid sequences in Figures 3, 6, 8, 9, 11, 13, 15, 17, 19, or polypeptide variants thereof.
- 15 7. A method according to any of Claims 1-6 wherein said cells are induced to differentiate by the addition of at least one agent selected from the group consisting of: retinoic acid; hexamethylene bisacetamide; bone morphogenetic proteins; bromodeoxyuridine; lithium; sonic hedgehog.
- 20 8. A method for modulating the differentiation of embryonic stem cells comprising:
- i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
 - a) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, 18.
 - 25 b) a nucleic acid molecule which hybridises to the nucleic acid in (ii) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and
 - c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
 - 30 ii) forming a culture comprising the cell identified in (i) above with an embryonic stem cell; and

- iii) growing said culture under conditions suitable for the maintenance and/or differentiation of said embryonic stem cell.
9. A method for modulating the differentiation of embryonic stem cells
5 comprising:
- i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
- a) a nucleic acid molecule as represented by the sequence in Figure 22;
- b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and
10 which encodes a ligand capable of binding a Wnt receptor; and
- c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
- ii) forming a culture comprising a cell identified in (i) above with an embryonic stem cell; and
- 15 iii) growing said culture under conditions suitable for the maintenance and/or differentiation of embryonic stem cells.
10. A method according to Claim 9 wherein said cell expresses Wnt-13 ligand.
- 20 11. A method according to any of Claims 9 or 10 wherein said cells are induced to differentiate by the addition of at least one agent selected from the group consisting of: retinoic acid; hexamethylene bisacetamide; bone morphogenetic proteins; bromodeoxyuridine; lithium; sonic hedgehog.
- 25 12. A method according to any of Claims 1-11 wherein said nucleic acid molecule encodes a ligand of human origin.
13. A method according to any of Claims 1-12 wherein said embryonic stem cells are of human origin.
- 30 14. A method according to any of Claims 8-13 wherein said transfected cell is a

mammalian cell.

15. A cell according to Claim 14 wherein said cell is selected from the group consisting of: a chinese hamster ovary cell; murine primary fibroblast cell; human
5 primary fibroblast cell; transformed mouse fibroblast cell-line STO.

16. A method for inhibiting the differentiation of embryonic stem cells comprising the steps of:

- 10 i) providing at least one polypeptide, or active fragment thereof, wherein said polypeptide is an inhibitor of the *Wnt* signalling pathway.
- iii) forming a culture comprising the polypeptide identified in (i) above with an embryonic stem cell; and
- iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

15

17. A method according to Claim 16 wherein said inhibitor is selected from the group consisting of the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus.

20

18. A method according to Claim 17 wherein said inhibitor is encoded by a nucleic acid molecule selected from the nucleic acid sequences represented by: Fig 57; Fig 59; Fig 61; Fig 63; Fig 65; Fig 67; Fig 69; Fig 71; Fig 73; Fig 75; Fig 77; Fig 79; Fig 81; Fig 83; Fig 85; Fig 87; Fig 89; Fig 91; Fig 93; Fig 95; Fig 97; Fig 99; Fig
25 101; or Fig 103.

19. A method for inhibiting the differentiation of embryonic stem cells comprising the steps of:

- 30 i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
 - a) a nucleic acid molecule encoding a Wnt inhibitory polypeptide;

- b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and which encodes a polypeptide capable of inhibiting *Wnt* signalling; and
 - c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
- 5 ii) forming a culture of the cell identified in (i) above with an embryonic stem cell; and
- iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.
- 10 20. A method according to Claim 19 wherein said cells express at least one Wnt inhibitory polypeptide selected from the group consisting of the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus.
- 15 21. A method according to Claim 19 wherein said cells express at least one Wnt inhibitory polypeptide encoded by a nucleic acid molecule selected from the nucleic acid sequences represented by : Fig 57; Fig 59; Fig 61; Fig 63; Fig 65; Fig 67; Fig 69; Fig 71; Fig 73; Fig 75; Fig 77; Fig 79; Fig 81; Fig 83; Fig 85; Fig 87; Fig 89; Fig 91; Fig 93; Fig 95; Fig 97; Fig 99; Fig 101; Fig or 103.
- 20 22. A cell or cell culture obtainable by the method according to any of Claims 1-21.
23. A therapeutic cell composition obtainable by the method according to any of
- 25 Claims 1-15.
24. Use of a cell according to Claim 23 for the manufacture of a composition for use in the treatment of a disease selected from the group consisting of: Parkinson's disease; Huntington's disease; motor neurone disease; heart disease;
- 30 diabetes; liver disease (eg cirrhosis); renal disease; AIDS.

25. A method of treatment of an animal, preferably a human, comprising administering a cell composition comprising embryonic stem cells which have been induced to differentiate into at least one cell-type by the method according to any of
5 Claims 1-14.

26. Condition medium obtained by culturing embryonic stem cells according to the method of any of Claims 1-21.

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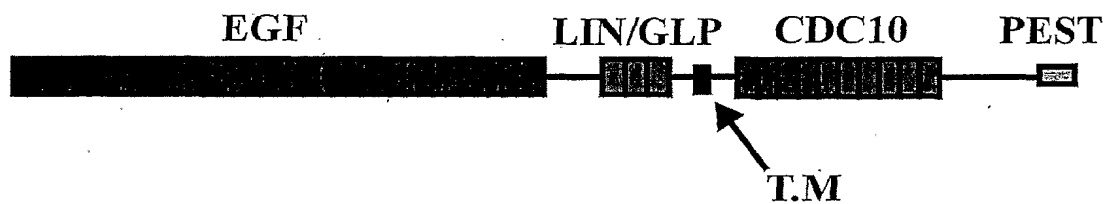
D.melanogaster**Notch****C.elegans****Lin-12****Glp-1****Vertebrate****Notch 1, 2****Notch 3****Notch 4**

Figure 1

Figure 2

GTCCAGCGGTACCATGGGCCGTCGGAGCGCGCTAGCCCTTGCCGTGGTCTCTGCCCTGC
TGTGCCAGGTCTGGAGCTCCGGCGTATTTGAGCTGAAGCTGCAGGAGTTCTGCAACAA
GAAGGGGCTGCTGGGGAACCGCAACTGCTGCCGCGGGGGCTCTGGCCCGCCTTGCGCC
TGCAGGACCTTCTTTTCGCGTATGCCTCAAGCACTACCAGGCCAGCGTGTACCCGGAGCC
ACCCTGCACCTACGGCAGTGCTGTACGCCAGTGCTGGGTGTGACTCCTTCAGCCTGC
CTGATGGCGCAGGCATCGACCCCGCCTTCAGCAACCCCATCCGATTCCCCTTCGGCTTC
ACCTGGCCAGGTACCTTCTCTCTGATCATTGAAGCCCTCCATACAGACTCTCCCGATGA
CCTCGCAACAGAAAACCCAGAAAGACTCATCAGCCGCCTGACCACACAGAGGCACCTC
ACTGTGGGAGAAGAATGGTCTCAGGACCTTCACAGTAGCGGCCGCACAGACCTCCGGT
ACTCTTACCGGTTTGTGTGTGACGAGCACTACTACGGAGAAGGTTGCTCTGTGTTCTGC
CGACCTCGGGATGACGCCTTTGGCCACTTCACCTGCGGGGACAGAGGGGAGAAGATGT
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TGACCAACATGGATACTGTGACAAACCAGGGGAGTGCAAGTGCAGAGTTGGCTGGCAG
GGCCGCTACTGCGATGAGTGCATCCGATACCCAGGTTGTCTCCATGGCACCTGCCAGC
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GAACTACTGTACTACCATAAGCCGTGCAGGAATGGAGCCACCTGCACCAACACGGGC
CAGGGGAGCTACACATGTTCTGCCGACCTGGGTATACAGGTGCCAACTGTGAGCTGG
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GTGTGAGCATGCACCCTGCCATAATGGGGCCACCTGCCACCAGAGGGGGCCAGCGCTAC
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ACCACCAGGGCCCATGGTGGTGGACCTCAGTGAGAGGCATATGGAGAGCCAGGGCGG
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GCTGTGCTGCTGTGGTGGTCTGCGTCCGGCTGAAGCTACAGAAACACCAGCCTCCACCT
GAACCTGTGGGGGAGAGACAGAAACCATGAACAACCTAGCCAATTGCCAGCGCGAG
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CACAGCAAACGTGACACCAAGTGCCAGTCAAGAGCTCTGCAGGAGAAGAGAAGATC
GCCCCAACACTTAGGGGTGGGGAGATTCTTGACAGAAAAAGGCCAGAGTCTGTCTACT
CTACTTCAAAGGACACCAAGTACCAGTCGGTGTATGTTCTGTCTGCAGAAAAGGATGA
GTGTGTTATAGCGACTGAGGTGTAAGATGGAAGCGATGTGGCAAAATTCCCATTTCTCT
CAAATAAAATTTCCAAGGATATAGCCCCGATGAATGCTGCTGAGAGAGGAAGGGAGAG
GAAACCCAGGGACTGCTGCTGAGAACCAGGTTTCAGGCGAAGCTGGTTCTCTCAGAGTT
AGCAGAGGCGCCCGACACTGCCAGCCTAGGCTTTGGCTGCCGCTGGACTGCCTGCTGG
TTGTTCCCATTTGCACTATGGACAGTTGCTTTGAAGAGTATATATTTAAATGGACGAGTG
ACTTGATTCATATAGGAAGCACGCACTGCCACACAGTCTATCTTGGATTACTATGAGCC
AGTCTTTCCTTGAAGTAGAAACACAACCTGCCTTTATTGTCTTTTTTGATACTGAGATGTG
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AAATTTTTGGTAAATATGTACAAAGGCACTTCGGGTCTATGTGACTATATTTTTTTGTAT
ATAAATGTATTTATGGAATATTGTGCAAATGTTATTTGAGTTTTTTACTGTTTTGTAAAT
GAAGAAATTCATTTTAAAAATATTTTTTCCAAAATAAATAATGAATACTACA

Figure 3

MGRRSALALAVVSALLCQVWSSGVFELKLQEFVNKKGLLGNRNCCRGSGPPCACRTFFR
VCLKHYQASVSPEPPCTYGSVTPVLGVDSFSLPDGAGIDPAFSNPIRFPFGFT,WPGTFSLIE
ALHTDSPDDLATENPERLISRLTTQRHLTVGEEWSQDLHSSGRDRLRYSYRFVCDHEYIGE
GCSVFCRPRDDAFGHFTCGDRGEKMCDPGWKQYCTDPICLPGCDDQHGYCDKPGECKC
RVGWQGRYCDCEIRYPGCLHGTCCQPWQCNCQEGWGGLFCNQDLNYCTHHKPCRNGAT
CTNTGQGSYTCSCRPGYTGANCELEVDECAPSPCKNGASCTDLEDSEFSCCTCPPGFYGKVCE
LSAMTCADGPCFNGGRCSDNPDGGYTCHCPLGFSGFNCEKKMDLCGSSPCSNGA KCVDL
GNSYLCRCQAGFSGRYCEDNVDDCASSPCANGGTCDSDVND FSCCTCPPGYTGKNCSAPVS
RCEHAPCHNGATCHQRGQRYMCECAQGYGGPNCQFLLPEPPP GPMVVDLSERHMESQGG
PFPWVAVCAGVVLVLLLLGCAAVVVCVRLKLQKHQPPPEPCGETETMNNLANCQREK
DVSVSIIGATQIKNTNKKADFDHGDHGAKKSSFVRYPTVDYNLVRDLKGDEATVRDTHSK
RDTKCQSQSSAGEEKIAPTLRGGEIPDRKRPESVYSTSKDTKYQSVYVLSAEKDECVIATEV

Figure 4

CGGGCAGAGGTGGAAGAGGGGGGAGCGCCTCAAAGAAGCGATCAGAATAATAAAAAGG
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AGTTTCGCCTGGCCGAGGTCCTACACTTTGCTGGTGGAGGCCTGGGATTCCAGTAATGA
CACTATTCAACCTGATAGCATAATTGAAAAGGCTTCTCACTCAGGCATGATAAACCTA
GCCGGCAATGGCAGACACTGAAACAAAACACAGGGATTGCCACTTCGAGTATCAGAT
CCGAGTGACCTGTGATGACCACTACTATGGCTTTGGCTGCAATAAGTTCTGTCTGCCA
GAGATGACTTCTTTGGACATTATGCCTGTGACCAGAACGGCAACAAAACCTTGCATGGA
AGGCTGGATGGGTCTCTGATTGCAACAAAGCTATCTGCCGACAGGGCTGCAGTCCCAAG
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ACTGCGACAAGTGCATCCCGCACCCAGGATGTGTCCACGGCACCTGCAATGAACCCTG
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Figure 5

CTGCGGCCGGCCCCGCGAGCTAGGCTGGGTTTTTTTTTTCTCCCCTCCCTCCCCCTTTT
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 GCGTATGGCTTTATTTTTTTGAACTCTTCTCATTACTTGTGCTTATAAGCCAAAATTA
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 CCCCATCTAGGGGAGCCTTGATTCCTTGTTATTCAACAGCAAGTGTGAATACTGCTTG
 AATAAACACCACTGGATTAATGGAAAAA

Figure 6

MRSPRTRGRSGRPLSLLLALLCALRAKVC GASGQFELELSMQNVNGELQNGNCCGGARN
 PGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFGSGSTPVIGGNTFNLKASRGNDRNRIV
 LPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQWQTLKQNTGVAHFYQ
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 HGSKLPGLDCRCQYGWQGLYCDKCIHPGCVHIGICNEPWQCLCETNWGGQLCDKDLNYC
 GTHQPCLNGGTCSTNIDDCSPNNCSHGGTCQDLVNGFKCVCPPQWTGKTCQLDANECEAKP
 CSPGWTGPTCSTNIDDCSPNNCSHGGTCQDLVNGFKCVCPPQWTGKTCQLDANECEAKP
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NRASDYFCKCPEDYEGKNCSHLKDHCRTPCEVIDSCTVAMASNDTPEGVRYISSNVCGPH
 GKCKSQSGGKFTCDCNKGFTGTYCHENINDCESNPCRNNGGTCIDGVNSYKICSDGWEGA
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 GYRCVCPFGHSGAKCQEVSGRPCITMGSVIPDGAKWDDDCNTCQCLNGRIACSKVWCGPR
 PCLLHKGHSECPSGQSCIPILDDQCFVHPCTGVGECRSSSLQPVKTKCTSDSYQDNCANIT
 FTFNKEMMSPGLTTEHICSELRLNLILKNVSAEYSIYIACEPSPSANNEIHVAISAEDIRDDGN
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 YWCLRKRKPGSHTHSASEDNTTNVREQLNQIKNPIEKHGANTVPIKDYENKNSKMSKIR
 THNSEVEEDDMDKHQKARFAKQPAYTLVDREEKPPNGTPTKHPNWTNKQDNRDLESAQ
 SLNRMEYTV

Figure 7

GGAGCGGGCGCGCGGCGGCGGGGCGCGGCGGGCGGGTTCGCGGGGGCAATGCGG
 GCGCAGGGCCGGGGCCTTCCCCCGGCGCTGCTGCTGCTGCTGGCGCTCTGGGTGCAG
 GCGGCGCGGGCCATGGGCTATTTTCGAGCTGCAGCTGAGCGCGCTGCGGAACGTGAACG
 GGGAGCTGCTGAGCGGCGCCTGCTGTGACGGCGCGGCCGACAACGCGCGCGGGGG
 CTGCGGCCACGACGAGTGCACACGTACGTGCGCGTGTGCCTTAAGAGTACCAGGCCA
 AGGTGACGCCCACGGGGCCCTGCAGCTACGGCCACGGCGCCACGCCCCTGCTGGGCG
 CAACTCCTTCTACCTGCCGCCGGCGGGCGCTGCGGGGGACCGAGCGCGCGCGCGGCC
 CGGGCCGGCGCGACCAAGACCCGGGCTTCGTGCTCATCCCCTTCCAGTTCGCCTGGCCG
 CGCTCCTTTACCCTCATCGTGGAGGCCTGGGACTGGGACAACGATAACACCCCGAATG
 AGGAGCTGCTGATCGAGCGAGTGTGCGCATGCCGCATGATCAACCCGGAGGACCGCTGG
 AAGAGCCTGCACTTCAGCGGCCACGTGGCGCACCTGGAGCTGCGATCCGCGTGCCTG
 CGACGAGAACTACTACAGCGCCACTTGCAACAAGTTCTGCCGGCCCCGCAACGACT
 TTTTCGGCCACTACACCTGCGACCAAGTACGGCAACAAGGCCTGCATGGACGGCTGGAT
 GGGCAAGGAGTGCAAGGAAGCTGTGTGTAAACAAGGGTGTAATTTGCTCCACGGGGG
 ATGCACCGTGCCTGGGGAGTGCAGTGCAGCTACGGCTGGCAAGGGAGGTTCTGCGATG
 AGTGTGTCCCCTACCCCGGCTGCGTGCATGGCAGTTGTGTGGAGCCCTGGCAGTGCAA
 CTGTGAGACCAACTGGGGCGGCCTGCTCTGTGACAAAGACCTGAACTACTGTGGCAGC
 CACCACCCCTGCACCAACGGAGGCACGTGCATCAACGCCGAGCCTGACCAGTACCGCT
 GCACCTGCCCTGACGGCTACTCGGGCAGGAACTGTGAGAAGGCTGAGCACGCCTGCAC
 CTCCAACCCGTGTGCCAACGGGGGCTCTTGCCATGAGGTGCCGTCCGGCTTCGAATGCC
 ACTGCCCATCGGGCTGGAGCGGGGCCACCTGTGCCCTTGACATCGATGAGTGTGCTTCG
 AACCCGTGTGCGGGCCGGTGGCACCTGTGTGGACCAGGTGGACGGCTTTGAGTGCATCT
 GCCCCGAGCAGTGGGTGGGGGCCACCTGCCAGCTGGACGTCAACGACTGTGAAGGGA
 AGCCATGCCTTAACGCTTTTTCTTGCAAAAACCTGATTGGCGGCTATTACTGTGATTGC
 ATCCCGGGCTGGAAGGGCATCAACTGCCATATCAACGTCAACGACTGTGCGGGGCAGT
 GTCAGCATGGGGCACCTGCAAGGACCTGGTGAACGGGTACCAGTGTGTGTGCCACGG
 GGCTTCGGAGGCCGGCATTGCGAGCTGGAACGAGACAAGTGTGCCAGCAGCCCTGCC
 ACAGCGGCGGCCTCTGCGAGGACCTGGCCGACGGCTCCACTGCCACTGCCCCCAGGGC
 TTCTCCGGGCCTCTCTGTGAGGTGGATGTGACCTTTGTGAGCCAAGCCCCTGCCGGAA
 CGGCGCTCGCTGCTATAACCTGGAGGGTGACTATTACTGCGCCTGCCCTGATGACTTTG
 GTGGCAAGAACTGCTCCGTGCCCCGCGAGCCGTGCCCTGGCGGGGCCTGCAGAGTGAT
 CGATGGCTGCGGGTCAGACGCGGGGCCTGGGATGCCTGGCACAGCAGCCTCCGGCGTG
 TGTGGCCCCCATGGACGCTGCGTCAGCCAGCCAGGGGGCAACTTTCTGTCATCTGTGA
 CAGTGGCTTTACTGGCACCTACTGCCATGAGAACATTGACGACTGCCTGGGCCAGCCCT
 GCCGCAATGGGGGCACATGCATCGATGAGGTGGACGCCTTCCGCTGCTTCTGCCCCAG
 CGGCTGGGAGGGCGAGCTCTGCGACACCAATCCCAACGACTGCCTTCCCGATCCCTGC

CACAGCCGCGGCCGCTGCTACGACCTGGTCAATGACTTCTACTGTGCGTGCGACGACG
GCTGGAAGGGCAAGACCTGCCACTCACGCGAGTTCCAGTGCGATGCCTACACCTGCAG
CAACGGTGGCACCTGCTACGACAGCGGCGACACCTTCCGCTGCGCCTGCCCCCGGC
TGGAAGGGCAGCACCTGCGCCGTCGCCAAGAACAGCAGCTGCCTGCCAACCCTGTG
TGAATGGTGGCACCTGCGTGGGCAGCGGGCCTCCTTCTCCTGCATCTGCCGGGACGG
CTGGGAGGGTTCGTA CTTGCACTCACAATACCAACGACTGCAACCCTCTGCCTTGCTACA
ATGGTGGCATCTGTGTTGACGGCGTCAACTGGTTCGCTGCGAGTGTGCACCTGGCTTC
GCGGGGCTGACTGCCGCATCAACATCGACGAGTGCCAGTCCTCGCCCTGTGCCTACG
GGGCCACGTGTGTGGATGAGATCAACGGGTATCGCTGTAGCTGCCACCCGGCCGAGC
CGGCCCCCGGTGCCAGGAAGTGATCGGGTTCGGGAGATCCTGCTGGTCCCGGGGCACT
CCGTTCCACACGGAAGCTCCTGGGTGGAAGACTGCAACAGCTGCCGCTGCCTGGATG
GCCGCGTGACTGCAGCAAGGTGTGGTGCGGATGGAAGCCTTGTCTGCTGGCCGGCCA
GCCCCGAGGCCCTGAGCGCCAGTGCCCACTGGGGCAAAGGTGCCTGGAGAAGGCCCC
AGGCCAGTGTCTGGACCACCCTGTGAGGCCTGGGGGGAGTGCGGCGCAGAAGAGCCA
CCGAGCACCCCTGCCTGCCACGCTCGGCCACCTGGACAATAACTGTGCCCGCCTCACC
TTGCATTTCAACCGTGACCACGTGCCCCAGGGCACCACGGTGGGCGCCATTTGCTCCGG
GATCCGCTCCCTGCCAGCCACAAGGGCTGTGGCACGGGACCGCCTGCTGGTGTGCTTT
GCGACCGGGCGTCCTCGGGGGCCAGTGCCGTGGAGGTGGCCGTGTCCTTCAGCCCTGC
CAGGGACCTGCCTGACAGCAGCCTGATCCAGGGCGCGGCCACGCCATCGTGGCCGCC
ATCACCAGCGGGGAACAGCTCACTGCTCCTGGCTGTCACCGAGGTCAAGGTGGAGAC
GGTTGTTACGGGCGGCTCTTCCACAGGTCTGCTGGTGCCTGTGCTGTGTGGTGCCTTCA
GCGTGCTGTGGCTGGCGTGCGTGGTCTGTGCGTGTGGTGGACACGCAAGCGCAGGAA
AGAGCGGGAGAGGAGCCGGCTGCCGCGGGAGGAGAGCGCCAACACAGTGGGCCCCGC
TCAACCCCATCCGCAACCCCATCGAGCGGCCGGGGGGCCACAAGGACGTGCTCTACCA
GTGCAAGAACTTCACGCCGCCGCCGCGCAGGGCGGACGAGGCGCTGCCCGGGCCCGC
CGGCCACGCGGCGTCAGGGAGGATGAGGAGGACGAGGATCTGGGCCGCGGTGAGGAG
GACTCCCTGGAGGCGGAGAAGTTCTCTCACACAAATTCACCAAAGATCCTGGCCGCTC
GCCGGGGAGGCCGGGCCACTGGGCCTCAGGCCCAAAGTGGACAACCGCGCGGTGAG
GAGCATCAATGAGGCCCGCTACGCCGGAAGGAGTAGGGGCGGCTGCGCTGGGCCGG
GACCCAGGGCCCTCGGTGGGAGCCATGCCGTCTGCCGGACCCGGAGCCGAGGCATGTG
CTAGTTTCTTTATTTTGTGTAAAAAAACCACCAAAAAACAAAAACCAAATGTTTATTTT
TACGTTTCTTTAACCTTGTATAAATTATTCAGTAACTGTCAGGCTGAAAACAATGGAGT
ATTCTCGGATAGTTGCTATTTTTGTAAAGTTTCCGTGCGTGGCACTCGCTGTATGAAAG
GAGAGAGCAAAGGGTGTCTGCGTTCGTACCAAATCGTAGCGTTTGTACCAGAGGTTG
TGCACTGTTTACAGAATCTTCTTTTATTCCTCACTCGGGTTTCTCTGTGGCTCCAGGCC
AAAGTGCCGCTGAGACCCATGGCTGTGTTGGTGTGGCCCATGGCTGTTGGTGGGACC
CGTGGCTGATGGTGTGGCCTGTGGCTGTCGGTGGGACTCGTGGCTGTCAATGGGACCTG
TGGCTGTCGGTGGGACCTACGGTGGTGGTGGGACCCTGGTTATTGATGTGGCCCTGGC
TGCCGGCACGGCCCGTGGCTGTTGACGCACCTGTGGTTGTTAGTGGGGCCTGAGGTCAT
CGGCGTGCCCAAGGCCGGCAGGTCAACCTCGCGCTTGTGGCCAGTCCACCCTGCCTG
CCGTCTGTGCTTCTCCTGCCAGAACGCCCGCTCCAGCGATCTCTCCACTGTGCTTTCA
GAAGTGCCCTTCTGCTGCGCAGTTCTCCCATCCTGGGACGGCGGCAGTATTGAAGCTC
GTGACAAGTGCCCTTACACAGACCCCTCGCAACTGTCCACGCGTGCCGTGGCACCAGG
CGCTGCCACCTGCCGGCCCCGGCCGCCCTCCTCGTGAAAGTGCAATTTTGTAAATGT
GTACATAFTAAAGGAAGCACTCTGTATATTTGATTGAATAATGCCACCAAAAAAAAAA
AAAAAAAAAAATTCCTGCCC

Figure 8

MRAQGRGAFPPALLLLLALWVQAARPMGYFELQLSALRNVNGELLSGACCDGDGRITRA
GGCGHDECDTYVRVCLKEYQAKVTPTGPCSYGHGATPVLGGNSFYLPAGAAAGDRARAR

PRAGGDQDPGFVVIPFQFAWPRSFTLIVEAWDWDNDTTPNEELLIERVSHAGMINPEDRWK
 SLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHYTCQYGNKACMDGWMG
 KECKEAVCKQGCNLLHGGCTVPGECRCSYGWQGRFCDECVPPGCVHGSCVEPWQCNCE
 NWGGLLCDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAEHACTSNPC
 ANGGSCHVPSGFECCHPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWV
 GATCQLDVNDCEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDCRGQCQHGGTCK
 DLVNGYQCVCPRGFGGRHCELERDKCASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVD
 VDLCEPSPCRNGARCYNLEGDYYCACPDDFGGKNCSVPREPCPGGACRVIDGCGSDAGPG
 MPGTAASGVCGPHGRCVVSQPGGNFSCICDSGFTGTYPCHENIDDLGQPCRNGGTCIDEVDA
 FRCFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDFYCACDDGWKGKTCHSREFQC
 DAYTCSNGGTCYDSGDTFRCACPPGWKGSTCAVAKNSSCLPNPCVNGGTCVGSASFSCI
 CRDGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDECQSSPC
 AYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTFPHGSSWVEDCNSCRCLDG
 RRDCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPPCEAWGECGAEPPST
 PCLPRSGHLDNNCARLTLHFNRDHVPQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRAS
 SGASAVEVAVSFSPARDLPDSSLIQGAHAIVAAITQRGNSSLLLAUTEVKVETVVTGGSS
 GLLVPVLCGAFSVLWLACVVLCVWWTRKRRKERERSRLPREESANNQWAPLNPINPIER
 PGGHKDVLVYQCKNFTPPPRRADEALPGPAGHAAVREDEEDEDLGRGEEDSLEAEKFLSHK
 FTKDPGRSPGRPAHWASGPKVDNRAVRSINEARYAGKE

Figure 9

MRSRTRGRPGRPLSLLLALLCALRAKVC GASGQFELEILSMQNVNGELQNGNCCGGVRN
 PGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFGSGSTPVIGGNTFNLKASRGNDNRNIV
 LPFSFAWPRS YTLLEAWDSSNDTIQPDSIIEKASHSGMINPSRQWQTLKQNTGIAHFEYQIR
 VTCDDHYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMMGPDCNKAICRQGCSPKH
 GSCKLPGDRCRCQYGWQGLYCDKCIHPGCVHGTCEPWPQCLCETNWGGQLCDKDLNYC
 GTHQPCLNRGTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCVPPQWTGKTCQLDANECEAKPC
 VNARSCKNLIASYYCDCLPGWMGQNCININDCLGQCQNDASCRDLVNGYRCICPPGYAG
 DHCERDIDECASNPCLNNGGHCQNEINRFQCLCPTGFSGNLCQLDIDYCEPNPCQNGAQCYN
 RASDYFCKCPEDYEGKNCSHLKDHCRTTTTCEVIDSCTVAMASNDTPEGVRYISSNVCGPHG
 KCKSQSGGKFTCDCNKGFTGTYPCHENINDCESNPCKNGGTCIDGVNSYKICSDGWEGAH
 CENNINDCSQNPCHYGGTCRDLVNDFYCDCKNGWKGTCHSRDSQCDEATCNGGTCY
 DEVDTFKCMCPGGWEGTTCNIARNSSCLPNPCHNGGTCVVNGDSFTVCCKEGWEGPICTQ
 NTNDCSPHPCYNSGTCVDGDNWYRCECAPGFAGPDCRININECQSSPCAFGATCVDEINGY
 QCICPPGHSGAKCHEVSGRSCITMGRVILDGAKWDDDCNTCQCLNGRVACSKVWCGPRPC
 RLHKSHNECPSGQSCIPVLDQCFVRPCTGVGECRSSSLQPVKTKCTSDSYQDNCANITFT
 FNKEMMSPGLTTEHICSELRLNLKKNVSAEYSIYIACEPSLSANNEIHVAISAEDIRDDGNP
 VKEITDKIIDLVSKRDGNSSLIAA VA EVRVQRRPLKNRTDFLVPLLSSVLTVAWVCCLVTAF
 YWCVRKRRKPSSHHSAPEDNTTNVREQLNQIKNPIEKHGANTVPIKDYENKNSKMSKIR
 THNSEVEEDMDKHQQKVRFAKQPVYTLVDREEKAPSGTPTKHPNWTNKQDNRDLESAQ
 SLNRMEYTV

Figure 10

TCGAGGCGGCGATGCGGGCACGCGGCTGGGGACGCCTGCCTCGGCGGCTGCTGCTGCT
 ACTGGTTCTGTGCGTGCAGGCGACGCGGCCCATGGGCTATTTTCGAGCTGCAGCTGAGC

GCGCTGCGGAACGTGAACGGGGAGCTGCTGAGCGGCGCCTGCTGTGACGGCGACGGC
CGGACGACGCGCGCGGGGGGCTGCGGCCGCGACGAGTGCGACACGTACGTGCGCGTG
TGCCTTAAGGAGTACCAGGCCAAGGTGACGCCCACGGGGCCCTGCAGCTACGGCTACG
GCGCCACGCCCCTGCTGGGTGGCAACTCCTTCTACCTGCCGCCGGCGGGCGCTGCGGG
GGACCGAGCGCGCGCGCGGTCTCGGACCGGCGGCCACCAGGACCCGGGCCTCGTCGTC
ATTCCCTTTTCAAGTTCGCCTGGCCGCGTTCTTTACCCCTCATCGTGGAGGCCTGGGACTG
GGACAATGACACCACTCCAGATGAGGAGCTGCTGATTGAGCGGGTGTGCGACGCTGGC
ATGATCAACCCCGAGGACCGCTGGAAGAGCCTGCACTTCAGCGGCCACGTGGCACACC
TGGAGCTGCAGATCCGAGTGCGCTGTGATGAGAACTACTACAGTGCCACCTGCAACAA
GTTCTGCCGGCCCCGCAACGACTTCTTTGGCCACTATACCTGCGACCAGTACGGCAACA
AGGCCTGCATGGATGGCTGGATGGGCAAAGAATGCAAAGAAGCCGTGTGTAAACAAG
GATGTAATTTGCTCCACGGGGGATGCACTGTGCCTGGGGAGTGCAGGTGCAGCTACGG
CTGGCAGGGCAAGTTCTGTGACGAGTGTGTCCCCTACCCTGGCTGCGTGCATGGCAGCT
GTGTGGAGCCCTGGCACTGTGACTGTGAGACCAACTGGGGTGGCCTGCTCTGCGACAA
AGACCTGAACTACTGTGGCAGCCACCACCCCTGTGTCAACGGGGGTACCTGCATCAAT
GCTGAGCCTGACCAATACCTCTGCGCCTGCCAGATGGCTACTTGGGCAAGAACTGTG
AGCGGGCTGAGCACGCCTGTGCCTCCAACCCGTGTGCCAATGGGGGCTCTTGCCACGA
AGTGCCATCTGGCTTTGAATGCCACTGTCCGTGAGGATGGAGCGGACCCACCTGTGCG
CTCGACATTGATGAGTGTGCCTCTAACCCATGTGCAGCGGGTGGTACCTGCGTGGATCA
GGTGGACGGCTTCGAGTGCATCTGCCCGGAGCAGTGGGTGGGGGCTACTTGCCAGCTG
GACGCCAATGAGTGTGAAGGGAAGCCGTGCCTTAATGCTTTTTTCTTGCAAAAACCTGAT
TGGCGGCTATTACTGTGATTGCCTCCCGGGCTGGAAGGGCATCAACTGCCAAATCAAC
ATCAACGATTGTCATGGGCAGTGTGAGCATGGGGGCACCTGCAAGGACCTGGTCAATG
GGTACCAGTGTGTGTGCCCCGCGGGGCTTTGGAGGTGCGCCATTGCGAACTAGAGTACGA
CAAGTGTGCCAGCAGCCCCCTGCCGCCGGGGTGGCATCTGCGAGGACCTGGTGGATGGC
TTCCGCTGCCACTGCCACGCGGGCCTCTCTGGGCTGCACTGTGAGGTGGACATGGATCT
CTGTGAACCAAGCCCCCTGCCTCAACGGTGTCTGCTGCTACAACCTTGAGGGTGACTION
ACTGCGCCTGCCCAGAAGACTTTGGTGGCAAGAACTGCTCAGTGCCAGGGACACATG
CCCTGGCGGGGCATGTAGAGTGATCGATGGCTGCGGGTTCGAGGCAGGGTCCAGGGCA
CGCGGTGTGCGACCCCTCTGGTATATGTGGCCCTCACGGGCACTGCGTTAGCCTGCCTGG
GGGAAACTTCTCCTGCATCTGTGACAGCGGCTTCACAGGCACCTACTGCCATGAAAAC
ATTGACGACTGCATGGGCCAGCCCTGCCGCAACGGGGGCACGTGCATTGACGAAGTGG
ACTCCTTCCGCTGCTTCTGCCCCAGTGGCTGGGAAGGAGAACTCTGTGACATCAATCCC
AACGACTGCCTCCCCGACCCCTGCCACAGCCGCGGCCGCTGCTATGACCTGGTCAATG
ACTTCTACTGTGCCTGTGACGATGGCTGGAAGGGCAAGACCTGCCACTCACGCGAGTT
CCAGTGTGACGCCTACACCTGCAGCAACGGTGGCACATGCTATGACAGCGGCGACACC
TTCCGCTGCGCGTGCCTCCGGGCTGGAAGGGCAGCACCTGCACCATCGCCAAGAACA
GCAGCTGTGTGCCAATCCCTGTGTGAATGGAGGCACCTGCGTGGGTAGCGGAGACTC
TTTCTCCTGCATCTGCCGGGATGGCTGGGAGGGCCGCACCTGCACACATAACACCAAT
GACTGCAACCCTCTGCCCTGCTATAACGGAGGCATCTGTGTTGATGGCGTCAACTGGTT
CCGCTGCGAGTGTGCGCCTGGCTTTGCGGGTCTGACTGCCGTATCAACATTGATGAGT
GCCAGTCCTCGCCCTGTGCCTACGGAGCCACGTGTGTGGATGAGATCAACGGGTACCG
CTGCAGCTGCCACCAAGGTCGTTCTGGCCCCAGGTGCCAGGAAGTGGTCATATTCACG
AGGCCCTGCTGGTCCC GGGAATGTCCTTCCCGCATGGGAGTTCTTGATGGAAGACT
GCAACAGCTGCCGCTGCCTGGATGGCCACCGGGATTGTAGCAAGGTATGGTGCGGATG
GAAGCCTTGCTGCTCTCTGGTCAGCCAGCGATCCGAGTGCCAGTGCCCCCAGGG
CAGCAATGTCAGGAGAAGGCCGTGGGTGAGTGTGCTTGCAGCCACCCTGTGAGAACTGGG
GGGAGTGTACAGCGGAGGAGCCTCTGCCACCCAGCACCCCTGTGAGCCACGGAGCAG
TCATTTGGACAACAACCTGTGCCCGACTCACACTGCGCTTCAACCGTGATCAAGTGCCTC
AGGGCACCAACCGTGGGCGCTATCTGCTCTGGAATCCGAGCCTTGCTGCCACGAGGGC
GGCGGCACACGACCGCCTCCTCCTGCTGCTTTGTGATCGAGCATCCTCGGGGGCCAGTG
CTGTGGAGGTGGCTATGTCTTTCAGCCCTGCAAGGGACCTGCCTGACAGCAGCCTGATC

CAGAGCACAGCCCACGCCATCGTGGCTGCTATCACTCAGAGAGGAAATAGCTCACTGC
 TGCTGGCTGTCACCGAGGTCAAGGTGGAAACAGTTGTTATGGGTGGCTCTTCCACAGGT
 CTGTTGGTGCCCGTGCTGTGCAGCGTGTTCAGTGTGCTGTGGCTCGCCTGTGTGGTTAT
 CTGCGTATGGTGGACACGAAAGCGCAGGAAAGAACGTGAGAGGAGCCGGCTACCACG
 GGATGAGAGCACCAACAACCAGTGGGCCCCGCTCAATCCCATCCGCAACCCCATTGAG
 CGGCCAGGCGGCAGCGGTCTGGGAACTGGGGGCCACAAGGACATACTCTACCAGTGC
 AAAA ACTTCACACCGCCGCCCGCAGGGCAGGGCAGGGCACTGCCCGGGCCAGCTGGCC
 ATGGGGCTGGTGGGGAGGACGAGGAGGATGAAGAGCTGAGCCGTGGAGATGGGGACT
 CCCCAGAGGCAGAGAAGTTCATCTCACACAAGTTCACCAAAGACCCAGCTGCTCCCT
 CGGAAGGCCAGCCTGCTGGGCTCCAGGGCCCCAAAGTGGACAACCGCGCCGTCAGAAG
 TACCAAGGACGTGCGCCGTGCTGGCAGGGAGTAGCCAGCCACCAGGCTGGCACCCAG
 AACCTTGCTGGCACCCACGCTGCCTGCCGGACCATAGGAGGCCAAGGCCGTGTGCATA
 GTTCTTTATTTTGTGTAAAAACAAAACCAAACCAAAAAACAAATGTTTATTTTAA
 CGTTTCTTTAACCTTGATATAAATTATTC AACGGCTGT CAGGCGGAAAACAACGGAGTAT
 TCTCGGATCATTGCTATTTTGTAAAGTTTCCGCGTCCGCACGCACTGTGGCAGGAGAG
 CAGGGCGTGTGTATGTGTGTGTGTGTGTGTGTCTCACC

Figure 11

MLCDKDLNYCGSHHPCVNNGGTCINAEPDQYLCACPDGYLGKNCERA EHACASNPCANGG
 SCHEVPSGFEC HCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATC
 QLDANECEGKPCLNAFSCKNLIGYYCDCLPGWKGINCQITINDCHGQVSAWGH LQGPVN
 GYQVCVPRGFGVRHCELEYDKCASSPCRRGGICEDLVDGFRCHCPRGLSGLHCEVDM DLC
 EPSPCFNGVRCYNLEGDYYCACPEDFGGKNC SVPRDTCPGGACRVIDGCGFEAGSRARGV
 APSGICGPHGHCVSLPGGNFSCICDSGFTGT YCHENIDDCMGQPCRNGGTCIDEVDSFRFC
 PSGWEGELCDINPNDCLPDPCHSRGR CYDLVNDFYCACDDGWKGK TCHSREFQCDAYTC
 SNGGTCYDSGDTFRCACPPGWKGSTCTIAKNSSCVPNPCVNNGGTCVGS GDSFSICICRDGWE
 GRTCTHNTNDCNPLPCYNNGGICVDGVHWFACECAPGF

Figure 12

GAAGGCCATGGTCTCCCCACGGATGTCCGGGCTCCTCTCCCAGACTGTGATCCTAGCGC
 TCATTTTCTCTCCCCCAGACACGGCCCGCTGGCGTCTTCGAGCTGCAGATCCACTCTTTC
 GGGCCGGGTCCAGGCCCTGGGGCCCCGCGGTCCCCCTGCAGCGCCCGGCTCCCCTGCC
 GCCTCTTCTTCAGAGTCTGCCTGAAGCCTGGGCTCTCAGAGGAGGCGCCGAGTCCCCG
 TGCGCCCTGGGCGCGGCGCTGAGTGCGCGCGGACCGGTCTACACCGAGCAGCCCGGAG
 CGCCCGCGCCTGATCTCCCACTGCCCGACGGGCTCTTGCAAGTGCCCTTCCGGGACG
 CCTGGCCTGGCACCTTCTCTTTCATCATCGAAACCTGGAGAGAGGAGTTAGGAGACCA
 GATTGGAGGGCCCGCCTGGAGCCTGCTGGCGCGCGTGGCTGGCAGGCGGCGCTTGGA
 GCCGGAGGCCCGTGGGCCCCGGGCATT CAGCGCGCAGGCGCCTGGGAGCTGCGCTTCTC
 GTACCGCGCGCGCTGCGAGCCGCTGCCGTCCGGACCGCGTGCACGCGCCTCTGCCGT
 CCGCGCAGCGCCCCCTCGCGGTGCGGTCCGGGACTGCGCCCCCTGCGCACCGCTCGAGG
 ACGAATGTGAGGCGCCGCTGGTGTGCCGAGCAGGCTGCAGCCCTGAGCATGGCTTCTG
 TGAACAGCCCGGTGAATGCCGATGCCTAGAGGGCTGGACTGGACCCCTCTGCACGGTC
 CCTGTCTCCACCAGCAGCTGCCTCAGCCCCAGGGGCCCGTCTCTGTCTACCACCGGATG
 CCTTGTCCTGGGCTGGGCCCTGTGACGGGAACCCGTGTGCCAATGGAGGCAGCTGT
 AGTGAGACACCCAGGTCTTTGAATGCACCTGCCCGCGTGGGTTCTACGGGCTGCGGT
 GTGAGGTGAGCGGGGTGACATGTGCAGATGGACCTGCTTCAACGGCG

GCTTGTGTGTCGGGGGTGCAGACCTGACTCTGCCTACATCTGCCACTGCCACCTGGT
 TTCCAAGGCTCCAACCTGTGAGAAGAGGGTGGACCGGTGCAGCCTGCAGCCATGCCGCA
 ATGGCGGACTCTGCCTGGACCGGGCCACGCCCTGCGCTGCCGCTGCCGCGCCGGCTTC
 GCGGGTCCTCGCTGCGAGCACGACCTGGACGACTGCGCGGGCCGCGCCTGCGCTAACG
 GCGGCACGTGTGTGGAGGGCGGCGCGCACCGCTGCTCCTGCCGCTGGGCTTCGGC
 GGCCGCGACTGCCGCGAGCGCGCGGACCCGTGCGCCGCGCGCCCCCTGTGCTCACGGC
 GGCCGCTGCTACGCCCACTTCTCCGGCCTCGTCTGCGCTTGCGCTCCCGGCTACATGGG
 AGCGCGGTGTGAGTTCCCAAGTGCACCCCGACGGCGCAAGCGCCTTGCCCGCGGCCCG
 CCGGGCCTCAGGCCCGGGGACCCTCAGCGCTACCTTTTGCTTCCGGCTCTGGGACTGCT
 CGTGGCCGCGGGCGTGGCCGGCGCTGCGCTCTTGCTGGTCCACGTGCGCCGCGGTGGC
 CACTCCCAGGATGCTGGGTCTCGCTTGCTGGCTGGGACCCCGGAGCCGTCAGTCCACG
 CACTCCCGGATGCACTCAACAACCTAAGGACGCAGGAGGGTTCGGGGATGGTCCGG
 CTCGTCCGTAGATTGGAATCGCCCTGAAGATGTAGACCCTCAAGGGATTTATGTCATAT
 CTGCTCCTTCCATCTACGCTCGGGAGGTAGCGACGCCCTTTTCCCCCGCTACACACT
 GGGCGCGCTGGGCAGAGGCAGCACCTGCTTTTTCCCTACCCTTCCTCGATTCTGTCCGT
 GAAATGAATTGGGTAGAGTCTCTGGAAGGTTTTAAGCCCATTTTCAGTTCTAACTTACT
 TTCATCCTATTTTGCATCCCTCTTATCGTTTTGAGCTACCTGCCATCTTCTCTT

Figure 13

MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGAPRSPCSARLPCRLFFRVC
 LKPLSEEAESPICALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFIE
 TWREELGDQIGPAWSLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVG
 TACTRLCRPRSAPSRCPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECCRCLEGWTG
 PLCTVPVSTSSCLSPRGPSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGFYGLR
 CEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLC
 LDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGRDCR
 ERADPCAARPCAHHGRCYAHFSGLVACAPGYMGARCEFPVHPDGASALPAAPPGLRPG
 DPQRYLLPPALGLLVAAGVAGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHALPDALNN
 LRTQEGSGDGPSSSVVDWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRAGQRQHLLF
 PYPSSILSVK

Figure 14

AAACCGGAACGGGGGCCCAACTTCTGGGGCCTGGAGAAGGGAAACGAAGTCCCCCCCCG
 GTTTCCCGAGGTGCCTTTTCTCGGGCATCCTTGGTTTCGGCGGGACTTCGCAGGGCGGA
 TATAAAGAACGGCGCCTTTGGGAAGAGGCGGAGACCGGCTTTAAAGAAAGAAGTCTTG
 GTCCTGCGGCTTGGGCGAGGCAAGGGCGAGGCAGGGCGCTTCTGCCGACGCTCCCCG
 TGGCCCTACGATCCCCCGCGCGTCCGCCGCTGTTCTAAGGAGAGAAGTGGGGGCCCG
 CAGGCTCGCGCGTGGAGCGAAGCAGCATGGGCAGTCGGTGCAGCGCTGGCCCTGGCGT
 GCTCTCGGCCTTGCTGTGTGTCAGGTCTGGAGCTCTGGGGTGTTCGAACTGAAGCTGCAGG
 AGTTCGTCAACAAGAAGGGGCTGCTGGGGAACCGCAACTGCTGCCGCGGGGGCGCGG
 GGCCACCGCCGTGCGCCTGCCGACCTTCTTCCGCGTGTGCCTCAAGCACTACCAGGCCA
 GCGTGTCCCCCGAGCCGCCCTGCACCTACGGCAGCGCCGTACCCCCGTGCTGGGCGT
 CGACTCCTTCAGTCTGCCCGACGGCGGGGGCGCCGACTCCGCGTTACGCAACCCCATC
 CGTTCCCCCTTCGGCTTCACCTGGCCGGGCACCTTCTCTCTGATTATTGAAGCTCTCC
 ACACAGATTCTCCTGATGACCTCGCAACAGAAAACCCAGAAAGACTCATCAGCCGCCT
 GGCCACCCAGAGGCACCTGACGGTGGGCGAGGAGTGGTCCCAGGACCTGCACAGCAG
 CGGCCGCACGGACCTCAAGTACTCTACCGCTTCGTGTGTGACGAACACTACTACGGAG
 AGGGCTGCTCCGTTTTCTGCCGTCCCCGGGACGATGCCTTCGGCCACTTCACCTGTGGG
 GAGCGTGGGGAGAAAGTGTGCAACCCTGGCTGGAAAGGGCCCTACTGCACAGAGCCG

ATCTGCCTGCCTGGATGTGATGAGCAGCATGGATTTTGTGACAAACCAGGGGAATGCA
 AGTGCAGAGTGGGCTGGCAGGGCCGGTACTGTGACGAGTGTATCCGCTATCCAGGCTG
 TCTCCATGGCACCTGCCAGCAGCCCTGGCAGTGCAACTGCCAGGAAGGCTGGGGGGGC
 CTTTTCTGCAACCAGGACCTGAACTACTGCACACACCATAAGCCCTGCAAGAATGGAG
 CCACCTGCACCAACACGGGGCCAGGGGAGCTACACTTCTCTTGCCGGCCTGGGTACACA
 GGTGCCACCTGCGAGCTGGGGATTGACGAGTGTGACCCAGCCCTTGTAAGAACGGAG
 GGAGCTGCACGGATCTCGAGAACAGCTACTCCTGTACCTGCCACCCGGCTTCTACGG
 CAAAATCTGTGAATTGAGTGCCATGACCTGTGCGGACGGCCCTTGCTTTAACGGGGGTC
 GGTGCTCAGACAGCCCCGATGGAGGGTACAGCTGCCGCTGCCCCGTGGGCTACTCCGG
 CTTCAACTGTGAGAAGAAAATTGACTACTGCAGCTCTTACCCTGTTCTAATGGTGCCA
 AGTGTGTGGACCTCGGTGATGCCTACCTGTGCCGCTGCCAGGCCGGCTTCTCGGGGAG
 GCACTGTGACGACAACGTGGACGACTGCGCCTCCTCCCCGTGCGCCAACGGGGGCACC
 TGCCGGGATGGCGTGAACGACTTCTCCTGCACCTGCCCGCCTGGCTACACGGGCAGGA
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 CCACCAGAGGGGGCACGGCTATGTGTGCGAATGTGCCCAGAGCTACGGGGGTCCCAACT
 GCCAGTTCCTGCTCCCCGAGCTGCCCCCGGGCCAGCGGTGGTGGACCTCACTGAGAA
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 GAACACCAACAAAAGGCGGACTTCCACGGGGACCACAGCGCCGACAAGAATGGCTTC
 AAGGCCCGCTACCCAGCGGTGGACATAACCTCGTGACAGGACCTCAAGGGTGACGACAC
 CGCCGTCAGGGACGCGCACAGCAAGCGTGACACCAGTGCCAGCCCCAGGGCTCCTCAG
 GGGAGGAGAAGGGGACCCCGACCACTCAGGGGTGGAGAAGCATCGAAAGAAAAA
 GGCCGGACTCGGGCTGTTCAACTTCAAAAGACACCAAGTACCAGTCGGTGTACGTCAT
 ATCCGAGGAGAAGGATGAGTGCGTCATAGCAACTGAGGTGTAAATGGAAGTGAGAT
 GGCAAGACTCCCGTTCTCTTAAATAAGTAAATTTCCAAGGATATATGCCCCAACGAA
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 TTTTGTATAATAAATGTATTTATGGAATATTGTGCCAATGTTATTTGAGTTTTTTACTGT
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 C

Figure 15

MGSRCALALAVLSALLCQVWSSGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFF
 RVCLKHYQASVSPEPPCTYGSATVPVLGVDSFSLPDGGGADSAFSNPIRFPFGFTWPGTFSLI
 IEALHTDSPDDLATENPERLISRLATQRHLTVGEEWSQDLHSSGRTDLKYSYRFVCDHEHY
 GEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTEPICLPGCDEQHGFCDKPGECK
 CRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGGLFCNQDLNYCTHHKPKKNGA
 TCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDLENSYSCTCPPGFYKICE
 LSAMTCADGPCFNGGRCSDSPDGGYSCRCPVGYSGFNCEKKIDYCSSSPCSNGAKCVDLG
 DAYLCRCQAGFSGRHCDDNVDDCASSPCANGGTCTRDGVNDFSCCTPPGYTGRCNSAPVSR
 CEHAPCHNGATCHQRGHGYVCECARSYGGPNCQFLLPELPPGPAVVDLTKLEGQGGPFP
 WVAVCAGVILVLMLLGCAAVVVCVRLRLQKHRPPADPCRGETETMNNLANCQREKDIS

VSIIGATQIKNTNKKADFDHSDKNGFKARYPAVDYNLVQDLKGDDTAVRDAHSKRD
TKCQPQGSSEEEKGTPPTLRGGEASERKRPDSCSTSKDTKYQSVYVISEEKDECVIATEV

Figure 16

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GATGCACTCATCAGCAAGATCGCCATCCAGGGCTCCCTAGCTGTGGGTGAGAACTGGT
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TCGGCCACTATGTGTGCCAGCCAGATGGCAACTTGTCTGCTGCCCGGTTGGACTGGG
GAATATTGCCAACAGCCTATCTGTCTTTCGGGCTGTGATGAACAGAATGGCTACTGCA
GCAAGCCAGCAGAGTGCCTCTGCCGCCAGGCTGGCAGGGCCGGCTGTGTAACGAATG
CATCCCCCACAATGGCTGTGCGCCACGGCACCTGCAGCACTCCCTGGCAATGTACTTGTG
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CCCATGCAAGAATGGGGCAACGTGCTCCAACAGTGGGCAGCGAAGCTACACCTGCACC
TGTCGCCCAGGCTACACTGGTGTGGACTGTGAGCTGGAGCTCAGCGAGTGTGACAGCA
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CCTGCTTCAATGGGGGCTCCTGCCGGGAGCGCAACCAGGGGGCCAACCTATGCTTGTGA
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CGGGGGACCATGCCAGGAAGTTTCCCCACAGTGACAAGAGCTTAGGAGAGAAGGCGC
CACTGCGGTTACACAGTGAAAAGCCAGAGTGCGGATATCAGCGATATGCTCCCCCAGG
GACTCCATGTACCAGTCTGTGTGTTTGATATCAGAGGAGAGGAATGAATGTGTCATTGC
CACGGAGGTATAA

Figure 17

MAAASRSASGWALLLLVALWQQRAAGSGVFQLQLQEFINERGVLASGRPCEPGCRTFFRV
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HAPGDDLPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTRLRYSYRVICSDNYYGDN
CSRLCKKRNDHFHGYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYCSKPAECLCRP
GWQGRLCNECIPHNGCRHGTCTPWQCTCDEGWGGLFCDQDLNYCTHHSPPCKNGATCSN
SGQRSYTCTCRPGYTGVDCLELSECDSNPCRNGGSCKDQEDGYHCLCPPGYGLHCEHS
TLSCADSPCFNGGSCRERNQGANYACECPPNFTGSNCEKKVDRCTSNPCANGGQCLNR

GPSRMCRCRPGFTGT YCELHVSDCARNPCA HGGTCHDLENGLMCTCPAGFSGRRC EVRTS
 IDACASSPCFN RATCYTDLSTDTFVCNCPYGFV GSRCEFPVGLPPSFPWVA VSLGVGLAVLL
 VLLGMVAVAVRQLRLRRPDDGSREAMNNLSDFQKDNLPAAQLKNTNQKKELEVDCGLD
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Figure 18

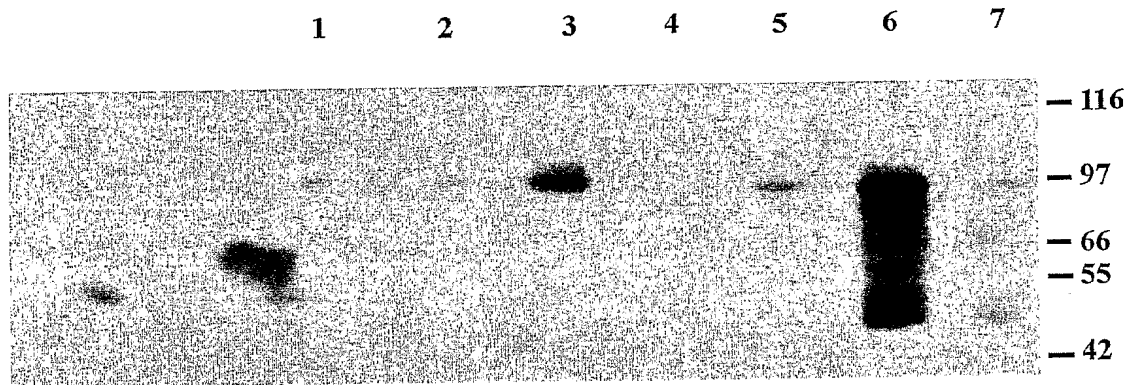
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Figure 19

MTPASRSACRWALLLLAVLWPQORAAGSGIFQLRLQEFVNQRGMLANGQSCEPGCRTFFR
ICLKHFQATFSEGPCTFGNVSTPVLGTNSFVVRDKNSGSGRNPLQLPFNFTWPGTFSLNIQA
WHTPGDDLRLPETSPGNLSLISQIIQGS LAVGKIWR TDEQNDTLTRLSYSYRVICSDNYYGES
SRLCKKRDDHFGHYECQPDGSLCLPGWTGKYCDQPICLSGCHEQNGYCSKPDECICRPG
WQGRLCNECIPHNGCRHGTCSIPWQCACDEGWGGLFCDQDLNYCTHSPCKNGSTCSNS
GPKGYTCTCLPGYTGEHCELGLSKCASNPCRNNGSCKDQENSYHCLCPPGYYGQHCEHST
LTCADSPCFNGGSCRERNQGSSYACECPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPSR
TCRCRPGFTGTHCELHISDCARSPCAHGGTCHDLENGPVCTCPAGFSGRRCVVRITHDACA
SGPCFNGATCYTGLSPNNFVCNCPYGFVGSRCFPVGLPPSFPWVAVSLGVGLVLLVLLV
MVVVAVRQLRLRRPDDESREAMNNLSDFQKDNLIPAAQLKNTNQKKELEVDCGLDKSNC
GKLQNHTLDYNLAPGLLGRGSM PGKYPHSDKSLGEKVPLRLHSEKPECRISAICSPRDSMY
QSVCLISEERNECVIATEV

Figure 20



Western blot analysis of Notch 2 expression in human germ cell tumour derived cell lines.

Western blot probed with antibody specific for the intracellular portion of human NOTCH2 and visualised using chemiluminescence. Lanes from left to right 1: BeWo, 2: TERA-1, 3: 833KE, 4: 2102 Ep 2A6, 5: 2102 Ep 4D3, 6: NTERA2/D1 8 days exposure to retinoic acid, 7: NTERA2/D1 EC cells. Molecular weight markers are indicated on the right in kDa. Notch2 protein product is visualized at approx 100 kDa

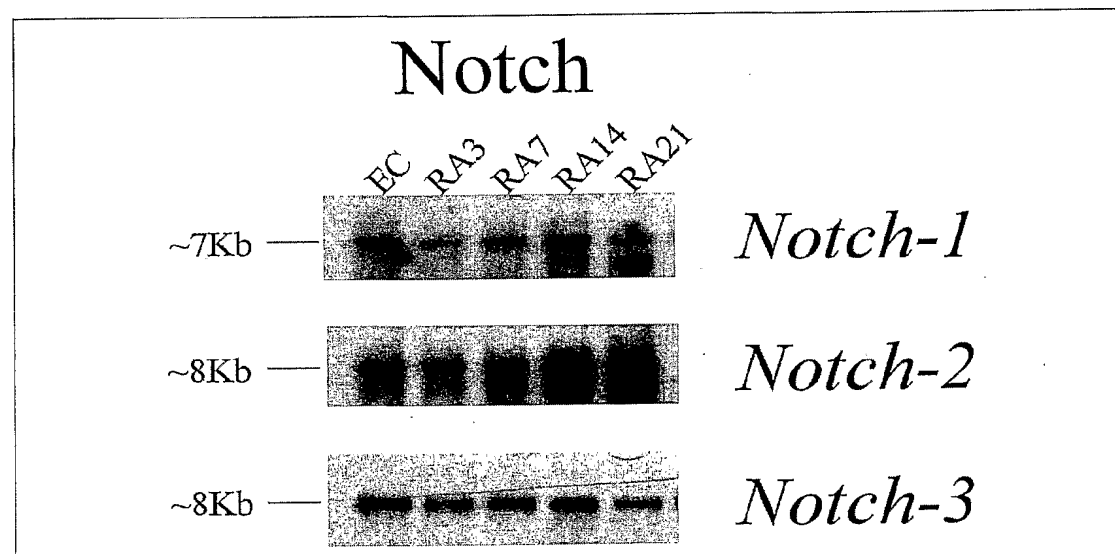
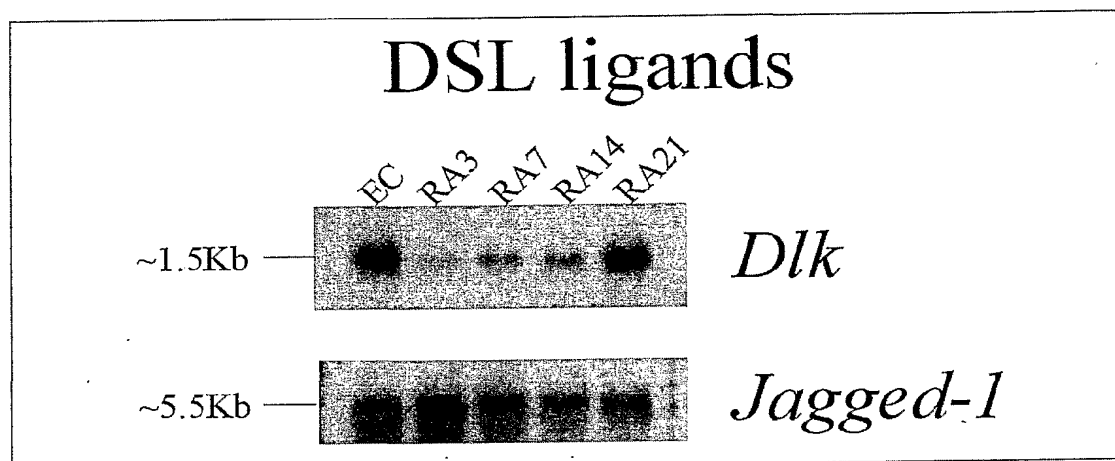
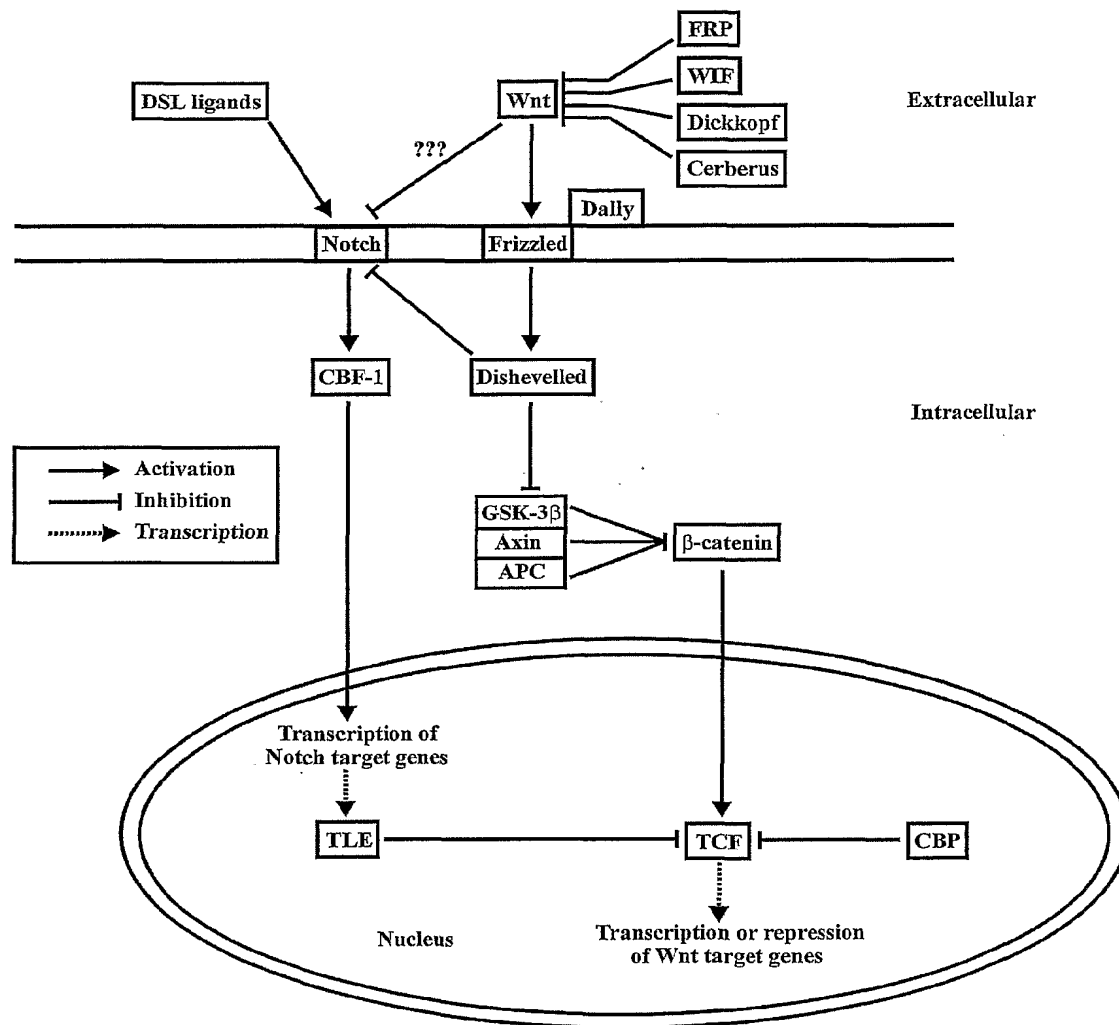


Figure 21

Figure 22

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AATTAAGTAGAAATAACTTTGCAAGGAGAGTCAAAGCTAAGGCCCCCGAAACCAGGCG
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ATTTATAGGTAGAGGCGACAAACCTACCGAGCCTGGTGATAGCTGGTTGTCCAAGATA
GAATCTTAGTTCAACTTTAAATTTGCCACAGAACCCTCTAAATCCCCCTTGTAATTTA
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GCATTTTGGAAATCAACTAAAACTGAAGGATCCTTGAGGACGGCAGTACCTGGCAT
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Fig 23



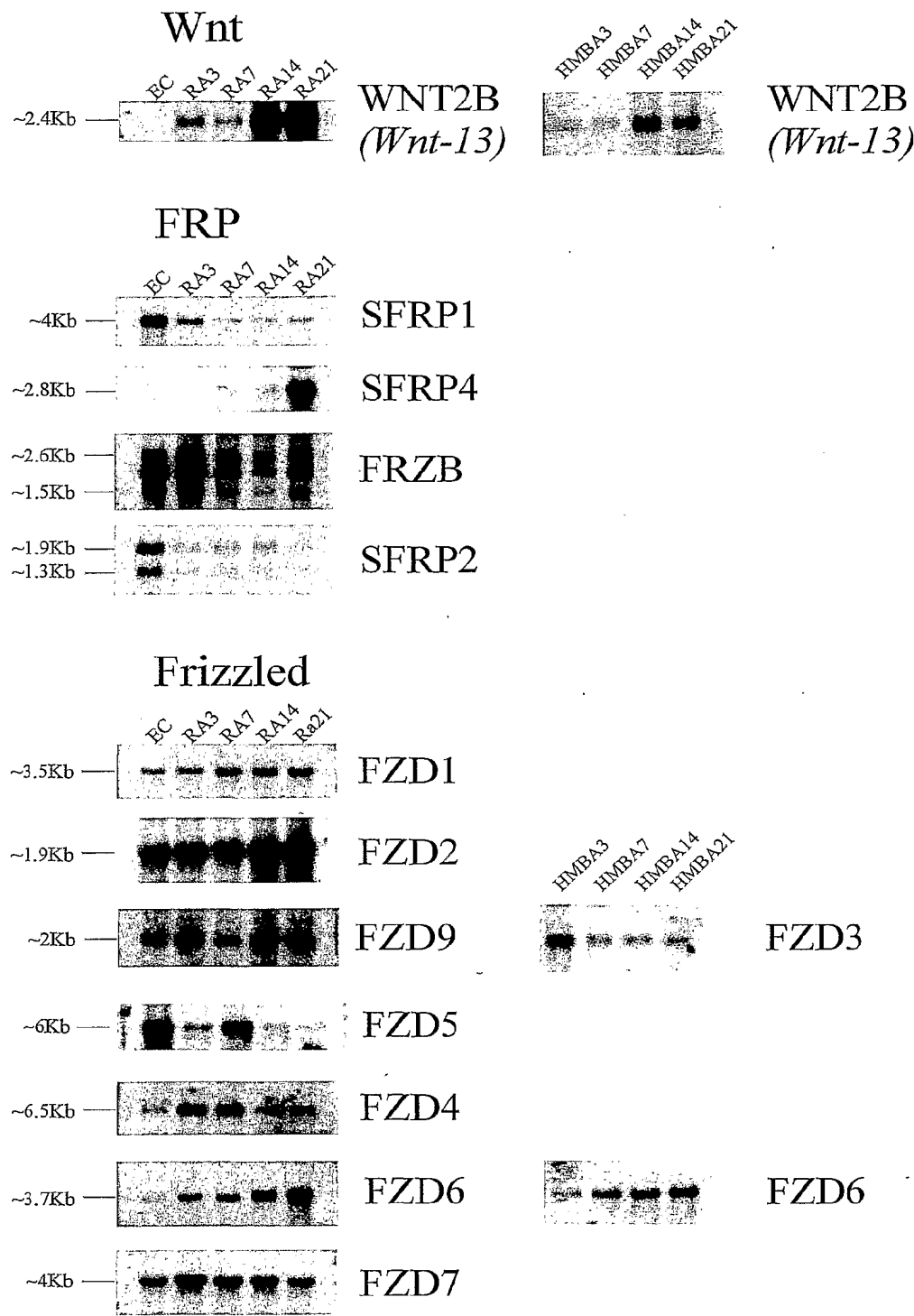


Figure 24

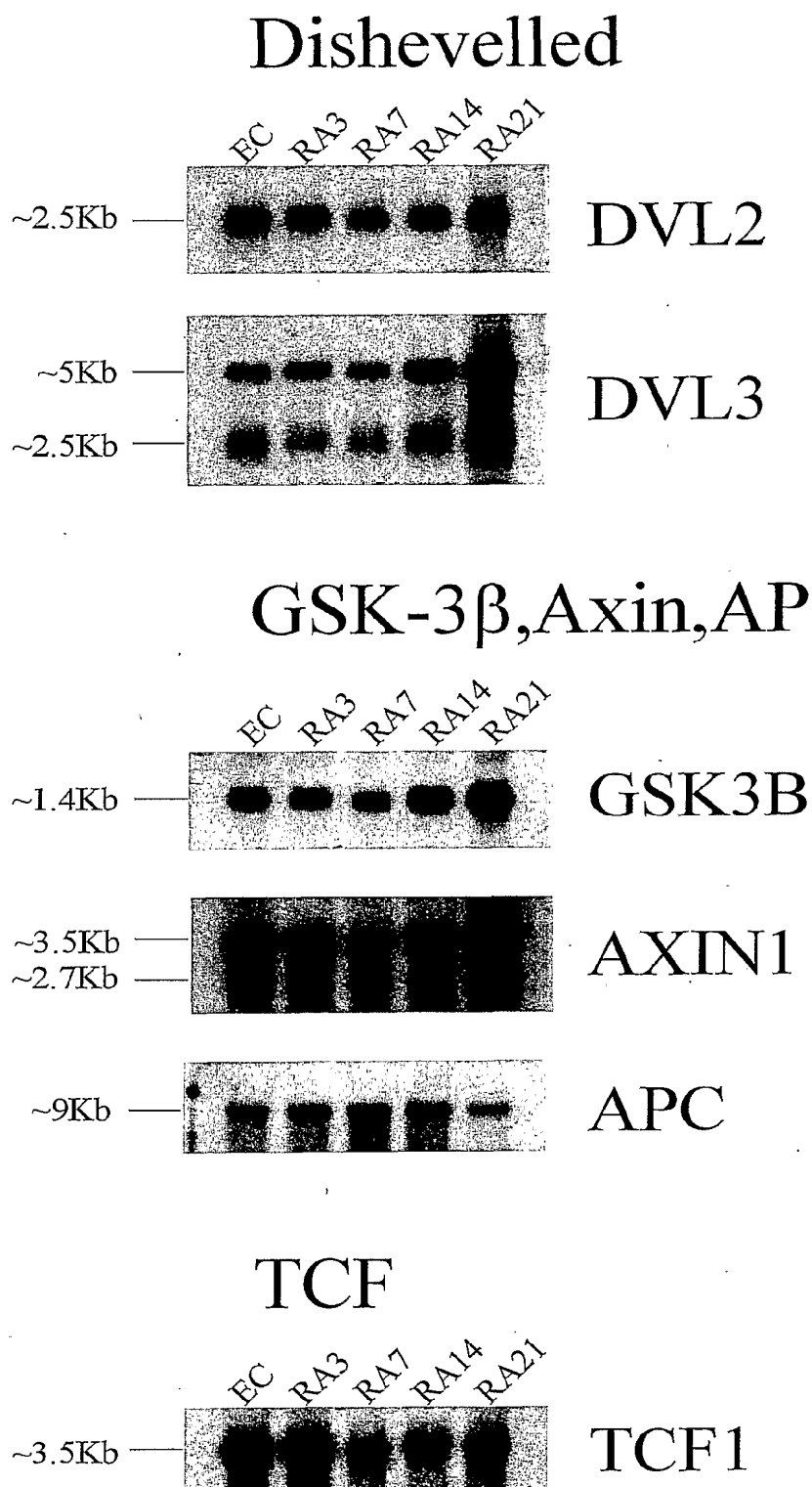


Figure 25

Figure 26

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ATGATGGCTCTGGGCGCAGCGGGAGCTACCCGGGTCTTTGTCGCGATGGTAGCGGGCGG
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CAGTCAGCGCCGCGCCGGGAATCCTGTACCCGGGCGGGAATAAGTACCAGACCATTGA
CAACTACCAGCCGTACCCGTGCGCAGAGGACGAGGAGTGCGGCACTGATGAGTACTGC
GCTAGTCCCACCCGCGGAGGGGACGCAAGGCGTGCAAATCTGTCTCGCCTGCAGGAAGC
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Figure 27

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ATTGCAGACTGTGAAGTTGTGTATTTAATGCATTATAGCATGGTGGAAAATAAGGTTCA
GATGCAGAAGAATGGCTAAAATAAGAAACGTGATAAGAATATAGATGATCACAAAAA
GGGAGAAAGAAAACATGAACCTGAATAGATTAGAATGGGTGACAAATGCAGTGCAGCC
AGTGTTCATTATGCAACTTGTCTATGTAAATAATGTACACATTTGTGGAAAATGCTA
TTATTAAGAGAACAAGCACACAGTGGAAATTACTGATGAGTAGCATGTGACTTTCCAA
GAGTTTAGGTTGTGCTGGAGGAGAGGTTTCCTTCAGATTGCTGATTGCTTATACAAATA
ACCTACATGCCAGATTTCTATTCAACGTTAGAGTTTAAACAAAATACTCCTAGAATAACT
TGTTATACAATAGGTTCTAAAAATAAAATTGCTAAACAAGAAATGAAAACATGGAGCA
TTGTTAATTTACAACAGAAAATTACCTTTTGATTTGTAACACTACTTCTGCTGTTCAATC
AAGAGTCTTGGTAGATAAGAAAAAAATCAGTCAATATTTCCAAATAATTGCAAAATAA
TGGCCAGTTGTTTAGGAAGGCCTTTAGGAAGACAAATAAATAACAAACAAACAGCCAC
AAATACTTTTTTTTCAAAATTTTAGTTTTACCTGTAATTAATAAGAACTGATACAAGAC
AAAAACAGTTTCCTTCAGATTCTACGGAATGACAGTATATCTCTTTATCCTATGTGAT
TCCTGCTCTGAATGCATTATATTTTCCAACTATACCCATAAATTGTGACTAGTAAAT
ACTTACACAGAGCAGAATTTTCACAGATGGCAAAAAAATTTAAAGATGTCCAATATAT
GTGGGAAAAGAGCTAACAGAGAGATCATTATTTCTTAAAGATTGGCCATAACCTGTAT
TTTGATAGAATTAGATTGGTAAATACATGTATTACATACATACTCTGTGGTAATAGAGAC
TTGAGCTGGATCTGTACTGCACTGGAGTAAGCAAGAAAATTGGGAAAACCTTTTTCGTTT
GTTCAAGTTTTTGGCAACACATAGATCATATGTCTGAGGCACAAGTTGGCTGTTTCATCTT
TGAAACCAGGGGATGCACAGTCTAAATGAATATCTGCATGGGATTTGCTATCATAATA
TTTACTATGCAGATGAATTCAGTGTGAGGTCCTGTGTCCGTACTATCCTCAAATTATTTA
TTTTATAGTGCTGAGATCCTCAAATAATCTCAATTTCAAGGAGGTTTCACAAAATGGACT

CCTGAAGTAGACAGAGTAGTGAGGTTTCATTGCCCTCTATAAGCTTCTGACTAGCCAAT
GGCATCATCCAATTTTCTTCCCAAACCTCTGCAGCATCTGCTTTATTGCCAAAGGGCTA
GTTTCGGTTTTCTGCAGCCATTGCGGTTAAAAAATATAAGTAGGATAACTTGTAACC
TGCATATTGCTAATCTATAGACACCACAGTTTCTAAATTCTTTGAAACCACTTTACTACT
TTTTTTAACTTAACTCAGTTCTAAATACTTTGTCTGGAGCACAAAACAATAAAAGGTT
ATCTTATAGTCGTGACTTTAAACTTTTGTAGACCACAATTCACTTTTTAGTTTTCTTTTA
CTTAAATCCCATCTGCAGTCTCAAATTTAAGTTCTCCCAGTAGAGATTGAGTTTGAGCC
TGTATATCTATTAAAAATTTCAACTTCCCACATATATTTACTAAGATGATTAAGACTTA
CATTTTCTGCACAGGTCTGCAAAAACAAAAATTATAAACTAGTCCATCCAAGAACCAA
AGTTTGTATAAACAGGTTGCTATAAGCTTGGTGAAATGAAAATGGAACATTTCAATCA
AACATTTCTATATAACAATTATTATATTTACAATTTGGTTTCTGCAATATTTTTCTTAT
GTCCACCCTTTTAAAAATTATTATTTGAAGTAATTTATTTACAGGAAATGTTAATGAGA
TGTATTTTCTTATAGAGATATTTCTTACAGAAAGCTTTGTAGCAGAATATATTTGCAGCT
ATTGACTTTGTAATTTAGGAAAAATGTATAATAAGATAAAATCTATTAAATTTTTCTCC
TCTAAAACTGAATTCAAAGC

Figure 28

ACACACAGGCGGCGGCTGCGGGCGCAGAGCGGAGATGCAGCGGCTTGGGGCCACCCT
GCTGTGCCTGCTGCTGGCGGCGGCGGTCCCCACGGCCCCCGCGCCCGCTCCGACGGCG
ACCTCGGCTCCAGTCAAGCCCGGCCCGGCTCTCAGCTACCCGCAGGAGGAGGCCACCC
TCAATGAGATGTTCCGCGAGGTTGAGGAACTGATGGAGGACACGCAGCACAAATTGCG
CAGCGCGGTGGAAGAGATGGAGGCAGAAGAAGCTGCTGCTAAAGCATCATCAGAAGT
GAACCTGGCAAACCTTACCTCCCAGCTATCACAATGAGACCAACACAGACACGAAGGTT
GGAAATAATACCATCCATGTGCACCGAGAAATTACAAAGATAACCAACAACCAGACTG
GACAAATGGTCTTTTTCAGAGACAGTTATCACATCTGTGGGAGACGAAGAAGGCAGAAG
GAGCCACGAGTGCATCATCGACGAGGACTGTGGGCCCAGCATGTACTGCCAGTTTGCC
AGCTTCCAGTACACCTGCCAGCCATGCCGGGGCCAGAGGATGCTCTGCACCCGGGACA
GTGAGTGCTGTGGAGACCAGCTGTGTGTCTGGGGTCACTGCACCAAAATGGCCACCAG
GGGCAGCAATGGGACCATCTGTGACAACCAGAGGGGACTGCCAGCCGGGGCTGTGCTGT
GCCTTCCAGAGAGGCCTGCTGTTCCCTGTGTGCACACCCTGCCCGTGGAGGGCGAGCT
TTGCCATGACCCCGCCAGCCGGCTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATG
GAGCCTTGGAACGATGCCCTTGTGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGC
CTGGTGTATGTGTGCAAGCCGACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCC
TGCTGCCCAGAGAGGTCCCCGATGAGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCG
CCAGGAGCTGGAGGACCTGGAGAGGAGCCTGACTGAAGAGATGGCGCTGGGGGAGCC
TGCGGCTGCCGCCGCTGCACTGCTGGGAGGGGAAGAGATTTAGATCTGGACCAGGCTG
TGGGTAGATGTGCAATAGAAATAGCTAATTTATTTCCCCAGGTGTGTGCTTTAGGCGTG
GGCTGACCAGGCTTCTTCCCTACATCTTCTTCCCAGTAAGTTTCCCCTCTGGCTTGACAGC
ATGAGGTGTTGTGCATTTGTTTCAGCTCCCCAGGCTGTTCTCCAGGCTTCACAGTCTGG
TGCTTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTTGCCACCCCTGTCCAGA
TTATTGGCTGCTTTGCCTCTACCAGTTGGCAGACAGCCGTTTGTCTACATGGCTTTGAT
AATTGTTTGAGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTCTGATTGTTTTGGG
GAAATGTGGAGAAGAGTGCCCTGCTTTGCAAACATCAACCTGGCAAAAATGCAACAAA
TGAATTTTCCACGCAGTTCTTTCCATGGGCATAGGTAAAGCTGTGCCTTCAGCTGTTGCA
GATGAAATGTTCTGTTCAACCTGCATTACATGTGTTTATTCATCCAGCAGTGTTGCTCAG

CTCCTACCTCTGTGCCAGGGCAGCATTTTTCATATCCAAGATCAATTCCCTCTCTCAGCA
CAGCCTGGGGAGGGGGTCATTGTTCTCCTCGTCCATCAGGGATCTCAGAGGCTCAGAG
ACTGCAAGCTGCTTGCCCAAGTCACACAGCTAGTGAAGACCAGAGCAGTTTCATCTGG
TTGTGACTCTAAGCTCAGTGCTCTCTCCACTACCCACACCAGCCTTGGTGCCACCAAA
AGTGCTCCCCAAAAGGAAGGAGAATGGGATTTTTCTTTTGAGGCATGCACATCTGGAA
TTAAGGTCAAACCTAATTCTCACATCCCTCTAAAAGTAACTACTGTTAGGAACAGCAGT
GTTCTCACAGTGTGGGGCAGCCGTCCTTCTAATGAAGACAATGATATTGACACTGTCCC
TCTTTGGCAGTTGCATTAGTAACTTTGAAAGGTATATGACTGAGCGTAGCATACAGGTT
AACCTGCAGAAACAGTACTTAGGTAAATTGTAGGGCGAGGATTATAAATGAAATTTGCA
AAATCACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAG
CAGGGCTGTGTGAAACATGGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCAC
TCCACAAATGATGTTTTTCAGGTGTCATGGACTGTTGCCACCATGTATTCTCCAGAGTT
CTTAAAGTTTAAAGTTGCACATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATG
TATAAACATAAGTTGCATTTAGAAATCAAGCATAAATCACTTCAACTGCTCTTCT

Figure 29

GACAAACAGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGA
GCAGCCTCGCTTTGGTGACGCACAGTGCTGGGACCCCTCCAGGAGCCCCGGGATTGAAG
GATGGTGGCGGCCGTCCTGCTGGGGCTGAGCTGGCTCTGCTCTCCCCTGGGAGCTCTGG
TCCTGGACTTCAACAACATCAGGAGCTCTGCTGACCTGCATGGGGCCCCGGAAGGGCTC
ACAGTGCCTGTCTGACACGGACTGCAATACCAGAAAGTTCTGCCTCCAGCCCCGCGAT
GAGAAGCCGTTCTGTGCTACATGTCTGTTGGGTTGCGGAGGAGGTGCCAGCGAGATGCCA
TGTGCTGCCCTGGGACACTCTGTGTGAACGATGTTTGTACTACGATGGAAGATGCAACC
CCAATATTAGAAAGGCAGCTTGATGAGCAAGATGGCACACATGCAGAAGGAACAACCT
GGGCACCCAGTCCAGGAAAACCAACCCAAAAGGAAGCCAAGTATTAAGAAATCACAA
GGCAGGAAGGGACAAGAGGGAGAAAAGTTGTCTGAGAACTTTTGACTGTGGCCCTGGAC
TTTGCTGTGCTCGTCATTTTTTGGACGAAAATTTGTAAGCCAGTCCTTTTGGAGGGACAG
GTCTGCTCCAGAAGAGGGCATAAAGACACTGCTCAAGCTCCAGAAATCTTCCAGCGTT
GCGACTGTGGCCCTGGACTACTGTGTGCAAGCCAATTGACCAGCAATCGGCAGCATGC
TCGATTAAGAGTATGCCAAAAAATAGAAAAGCTATAAATATTTCAAAATAAAGAAGAA
TCCACATTGCATTTGAG

Figure 30

ATGGGGCTCTGGGCGCTGTTGCCTGGCTGGGTTTCTGCTACGCTGCTGCTGGCGCTGGC
CGCTCTGCCCCGAGCCCTGGCTGCCAACAGCAGTGCCGATGGTGGGGTATTGTGAAC
GTAGCCTCCTCCACGAACCTGCTTACAGACTCCAAGAGTCTGCAACTGGTACTCGAGCC
CAGTCTGCAGCTGTTGAGCCGCAAACAGCGGCGCCTGATACGCCAAAATCCGGGGATC
CTGCACAGCGTGAGTGGGGGGCTGCAGAGTGCCGCTGCGCGAGTGCAAGTGGCAGTTCC
GGAATCGCCGCTGGAACGTGCCACTGCTCCAGGGCCCCACCTCTTCGGCAAGATCGTC
AACCGAGGCTGTGAGAAACGGCGTTTATCTTCGCTATCACCTCCGCCGGGGTACCC
ATTCCGGTGGCGCGCTCCTGCTCAGAAGGTTCCATCGAATCCTGCACGTGTGACTACCGG
CGGCGCGGCCCCGGGGGCCCCGACTGGCACTGGGGGGGCTGCAGCGACAACATTGACT
TCGGCCGCTCTTCGGCCGGGAGTTCTGTGACTCCGGGGAGAAGGGGCGGGACCTGCG
CTTCCTCATGAACCTTCACAACAACGAGGCAGGCCGTACGACCGTATTCTCCGAGATG
CGCCAGGAGTGCAAGTGCCACGGGATGTCCGGCTCATGCACGGTGCACAGTGTGCTGGA
TGCGGCTGCCACGCTGCGCGCCGTGGGCGATGTGCTGCGCGACCGCTTCGACGGCGC

CTCGCGCGTCCTGTACGGCAACCGCGGCAGCAACCGCGCTTCGCGAGCGGAGCTGCTG
CGCCTGGAGCCGGAAGACCCGGCCACAAACCGCCCTCCCCACGACCTCGTCTACT
TCGAGAAATCGCCCAACTTCTGCACGTACAGCGGACGCCTGGGCACAGCAGGCACGGC
AGGGCGCGCCTGTAAACAGCTCGTCGCCCCGCGCTGGACGGCTGCGAGCTGCTCTGCTGC
GGCAGGGGCCACCGCACGCGCACGCAGCGCTCACCGAGCGCTGCAACTGCACCTTCC
ACTGGTGCTGCCACGTCAGCTGCCGCAACTGCACGCACACGCGCGTACTGCACGAGTG
TCTGTGA

Figure 31

MGLWALLPGWVSATLLALLAALPAALANSSGRWWGIVNVASSTNLLTDSKSLQLVLEPS
LQLLSRKQRRLIRQNPILHSVSGGLQSAVRECKWQFRNRRWNCPTAPGPHLFGKIVNRGC
RETAFIFAITSAGVTHSVARSCSEGSIESCTCDYRRRGPPGPDWHWGGCSDNIDFGRFLGRE
FVDSGEKGRDLRFLMNLHNNEAGRRTTVFSEMRQECKCHGMSGSCVTRTCWMRLPTLRAV
GDVLRDRFDGASRVLYGNRGSNRASRAELLRLEPEDPAHKPPSPHDLVYFEKSPNFCTYSG
RLGTAGTAGRACNSSSPALDGCELLCCGRGHRTRTQRVTERCNCTFHWCCHVSCRNCTHT
RVLHECL

Figure 32

AGCAGAGCGGACGGGCGCGCGGGAGGCGCGCAGAGCTTTCGGGCTGCAGGCGCTCGC
TGCCGCTGGGGAATTGGGCTGTGGGCGAGGCGGTCCGGGCTGGCCTTTATCGCTCGCT
GGGCCCATCGTTTGAAACTTTATCAGCGAGTCGCCACTCGTCGCAGGACCGAGCGGGG
GGCGGGGGCGCGGCGAGGCGGCGGCCGTGACGAGGCGCTCCCGGAGCTGAGCGCTTC
TGCTCTGGGCACGCATGGCGCCCGCACACGGAGTCTGACCTGATGCAGACGCAAGGGG
GTTAATATGAACGCCCTCTCGGTGGAATCTGGCTCTGGCTCCCTCTGCTCTTGACCTG
GCTACCCCCGAGGTCAACTCTTCATGGTGGTACATGAGAGCTACAGGTGGCTCCTCCA
GGGTGATGTGCGATAATGTGCCAGGCCTGGTGAGCAGCCAGCGGCAGCTGTGTACCG
ACATCCAGATGTGATGCGTGCCATTAGCCAGGGCGTGGCCGAGTGACAGCAGAATGC
CAGCACCAGTTCGCCAGCACCGCTGGAATTGCAACACCCTGGACAGGGATCACAGCC
TTTTTGGCAGGGTCTACTCCGAAGTAGTCGGGAATCTGCCTTTGTTTATGCCATCTCCT
CAGCTGGAGTTGTATTTGCCATCACCAGGGCCTGTAGCCAAGGAGAAGTAAAATCCTG
TTCCTGTGATCCAAAGAAGATGGGAAGCGCCAAGGACAGCAAAGGCATTTTTGATTGG
GGTGGCTGCAGTGATAACATTGACTATGGGATCAAATTTGCCCGCGCATTTGTGGATGC
AAAGGAAAGGAAAGGAAAGGATGCCAGAGCCCTGATGAATCTTCACAACAACAGAGC
TGGCAGGAAGGCTGTAAAGCGGTTCTTGAAACAAGAGTGCAAGTGCCACGGGGTGAG
CGGCTCATGTACTCTCAGGACATGCTGGCTGGCCATGGCCGACTTCAGGAAAACGGGC
GATTATCTCTGGAGGAAGTACAATGGGGCCATCCAGGTGGTCATGAACCAGGATGGCA
CAGGTTTCACTGTGGCTAACGAGAGGTTTAAGAAGCCAACGAAAAATGACCTCGTGTA
TTTTGAGAATTCTCCAGACTACTGTATCAGGGACCGAGAGGCAGGCTCCCTGGGTACA
GCAGGCCGTGTGTGCAACCTGACTTCCCGGGGCATGGACAGCTGTGAAGTCATGTGCT
GTGGGAGAGGCTACGACACCTCCCATGTACCCGGATGACCAAGTGTGGGTGTAAGTT
CCACTGGTGCTGCGCCGTGCGCTGTGAGGACTGCCTGGAAGCTCTGGATGTGCACACA
TGCAAGGCCCCCAAGAACGCTGACTGGACAACCGCTACATGACCCAGCAGGCGTCAC
CATCCACCTTCCCTTCTACAAGGACTCCATTGGATCTGCAAGAACTGGACCTTTGGG
TTCTTTCTGGGGGGATATTTCCCTAAGGCATGTGGCCTTTATCTCAACGGAAGCCCCCTC
TTCCTCCCTGGGGGGCCCCAGGATGGGGGGCCACACGCTGCACCTAAAGCCTACCCTAT

TCTATCCATCTCCTGGTGTCTGCAGTCATCTCCCCTCCTGGCGAGTTCTCTTTGGAAT
AGCATGACAGGCTGTTTCAGCCGGGAGGGTGGTGGGCCCAGACCACTGTCTCCACCCAC
CTTGACGTTTCTTCTTTCTAGAGCAGTTGGCCAAGCAGAAAAAAGTGTCTCAAAGG
AGCTTTCTCAATGTCTTCCCACAAATGGTCCAATTAAGAAATTCCATACTTCTCTCAG
ATGGAACAGTAAAGAAAGCAGAATCAACTGCCCTGACTTAACCTTTAACTTTGAAAA
GACCAAGACTTTTGTCTGTACAAGTGGTTTTACAGCTACCACCCTTAGGGTAATTGGTA
ATTACCTGGAGAAGAATGGCTTTCAATACCCTTTTAAGTTTAAAATGTGTATTTTCAA
GGCATTATTGCCATATTAATAATCTGATGTAACAAGGTGGGGACGTGTGTCCCTTGGTA
CTATGGTGTGTTGTATCTTTGTAAGAGCAAAAGCCTCAGAAAGGGATTGCTTTCATTA
CTGTCCCCTTGATATAAAAAATCTTTAGGGAATGAGAGTTCCTTCTCACTTAGAATCTG
AAGGGAATTAAGAAAGATGAATGGTCTGGCAATATTCTGTAAGTATTGGGTGAATA
TGGTGGAAAATAATTTAGTGGATGGAATATCAGAAGTATATCTGTACAGATCAAGAAA
AAAAGGAAGAATAAAATTCCTATATCAT

Figure 33

MNAPLGGIWLWLPLLLTWLTPEVNSSWWYMRATGGSSSRVMCDNVPGLVSSQRQLCHRH
PDVMRAISQGVAEWTAECQHQRQHRWNCNTLDRDHSFLFRVLLRSSRESAFVYAISSAG
VVFAITRACSQGEVKSCSCDPKKMGSAKDSKGIFDWGGCSDNIDYGIKFARAFVDAKERK
GKDARALMNLHNNRAGRKA VKRFLKQECKCHGVSGSCTLRTCWLAMADFRKTGDYLW
RKYNGAIQVVMNQDGTGFTVANERFKKPTKNLTVYFENSPDYCIRDREAGSLGTAGRVC
NLTSRGMDSCCEVMCCGRGYDTSHVTRMTKCGCKFWCCAVRCQDCLEALDVHTCKAPK
NADWTTAT

Figure 34

CGGGAGTCTTCGGGGAGCTATGCTGAGACCGGGTGGTGC GGAGGAAGCTGCGCAGCTC
CCGCTTCGGCGCGCCAGCGCCCCGGTCCCTGTGCGGTGCGCCGCGGGCCCCGACGGCTC
CCGGGCTTCGGCCCGCCTAGGTCTTGCCCTGCCTTCTGCTCCTGCTGCTGCTGACGCTGC
CGGCCCCGCTAGACACGTCCTGGTGGTACATTGGGGCACTGGGGGCACGAGTGATCTG
TGACAATATCCCTGGTTTGGTGAGCCGGCAGCGGCAGCTGTGCCAGCGTTACCCAGAC
ATCATGCGTTCAAGTGGGCGAGGGTGCCCCGAGAATGGATCCGAGAGTGTCAGCACCAAT
TCCGCCACCACCGCTGGAAGTGTACCACCCTGGACCGGGACCACACCGTCTTTGGCCGT
GTCATGCTCAGAAGTAGCCGAGAGGCAGCTTTTGTATATGCCATCTCATCAGCAGGGG
TAGTCCACGCTATTACTCGCGCCTGTAGCCAGGGTGAAGTGAAGTGTGTGCAGCTGTGAC
CCCTACACCCGTGGCCGACACCATGACCAGCGTGGGGACTTTGACTGGGGTGGCTGCA
GTGACAACATCCACTACGGTGTCCGTTTTGCCAAGGCCTTCGTGGATGCCAAGGAGAA
GAGGCTTAAGGATGCCCGGGCCCTCATGAAGTTACATAATAACCGCTGTGGTTCGCACG
GCTGTGCGGCGGTTTTCTGAAGCTGGAGTGTAAGTGCCATGGCGTGAGTGGTTCCTGTAC
TCTGCGCACCTGCTGGCGTGCACTCTCAGATTTCCGCCGCACAGGTGATTACCTGCGGC
GACGCTATGATGGGGCTGTGCAGGTGATGGCCACCCAAGATGGTGCCAACCTCACCGC
AGCCCGCCAAGGCTATCGCCGTGCCACCCGGACTGATCTTGTCTACTTTGACAACCTCTC
CAGATTACTGTGTCTTGGACAAGGCTGCAGGTTCCCTAGGCACTGCAGGCCGTGTCTGC
AGCAAGACATCAAAAGGAACAGACGGTTGTGAAATCATGTGCTGTGGCCGAGGGTAC
GACACAACCTCGAGTCACCCGTGTTACCCAGTGTGAGTGCAAATTCCTACTGGTGTGTGC
TGTACGGTGCAAGGAATGCAGAAATACTGTGGACGTCCATACTTGCAAAGCCCCCAAG
AAGGCAGAGTGGCTGGACCAGACCTGAACACACAGATACTCACTCATCCCTCCAATT
CAAGCCTCTCAACTCAAAAGCACAAGATCCTTGCATGCACACCTTCCTCCACCCTCCAC
CCTGGGCTGTACCGCTTCTAATTAAGGATGTAGAGAGTAATCCATAGGGACCATGGTG
TCCTGGCTGGTTCCTTAGCCCTGGGAAGGAGTTGTGAGGGGATATAAGAACTGTGCA
AGCTCCCTGATTTCCCGCTCTGGAGATTTGAAGGGAGAGTAGAAGAGATAGGGGGTCT
TAGAGTGAAATGAGTTGCACTAAAGTACGTAGTTGAGGCTCCTTTTTTCTTTCTTTGC

ACCAGCTTCCCGACACTTCTTGGTGTGCAAGAGGAAGGGTACCTGTAGAGAGCTTCTTT
TTGTTTCTACCTGGCCAAAGTTAGATGGGACAAAGATGAATGGCATGTCCCTTCTCTGA
AGTCCGTTTGAGCAGAACTACCTGGTACCCCGAAAGAAAAATCTTAGGCTACCACATT
CTATTATTGAGAGCCTGAGATGTTAGCCATAGTGGACAAGGTTCCATTACATGCTCAT
ATGTTTATAAACTGTGTTTTGTAGAAGAAAAAGAATCATAACAATACAAACACACATT
CATTCTCTCTTTTCTCTCTACCATTCTCAACCTGTATTGGACAGCACTGCCTCTTTTGCT
TACTTGCTGCCTGTTCAAACCTGAGGTGGAATGCAGTGGTTCCCATGCTTAACAGATCAT
TAAACACCCCTAGAACACTCCTAGGATAGATTAATGT

Figure 35

MLDGLGVVAISIFGIQLKTEGSLRTAVPGIPTQSAFNKCLQRYIGALGARVICDNIPGLVSRQ
RQLCQRYPDIMRSVGEAREWIRECQHQRHHRWNCTTLDRDHTVFGRVMLRSSREAAF
VYAISAGVIHAITRACSQGELSVCSDDPYTRGRHHDQRGTFDWGGCSDNIHYGVRFAKAF
VDAKEKRLKDARALMNLHNNRCGRТАVRRFVKLECKCHGVSGSCTLRTCWRALSDFRRT
GDYLRRRYDGAVQVMATQDGANFTAARQGYRRATRSDLVYFDNSPDYCVLDKAAGSLG
TAGRVCSKTSKGTDGCEIMCCGRGYDTTRVTRVTQCECKFWCCAVRCKECRNTVDVHT
CKAPKKAEWLDQT

Figure 36

GCGCTTCTGACAAGCCCGAAAGTCATTTCCAATCTCAAGTGGACTTTGTTCCAACCTATT
GGGGGCGTCGCTCCCCCTCYTCATGGTCGCGGGCAAACCTTCCTCCTCGGCGCCTCTTCT
AATGGAGCCCCACCTGCTCGGGCTGCTCCTCGGCCTCCTGCTCGGTGGCACCAGGGTCC
TCGCTGGCTACCCAATTTGGTGGTCCCTGGCCCTGGGCCAGCAGTACACATCTCTGGGC
TCACAGCCCCCTGCTCTGCGGCTCCATCCCAGGCCTGGTCCCCAAGCAACTGCGCTTCTG
CCGCAATTACATCGAGATCATGCCCAGCGTGGCCGAGGGCGTGAAGCTGGGCATCCAG
GAGTGCCAGCACCAGTTCCGGGGCCGCGCTGGAAGTGCACCACCATAGATGACAGCC
TGGCCATCTTTGGGCCCGTCCTCGACAAAGCCACCCGCGAGTCGGCCTTCGTTACAGCC
ATCGCCTCGGCCGGCGTGGCCTTCGCCGTACCCGCTCCTGCGCCGAGGGCACCTCCAC
CATTTGCGGCTGTGACTCGCATCATAAGGGGGCCGCTGGCGAAGGCTGGAAGTGGGGC
GGCTGCAGCGAGGACGCTGACTTCGGCGTGTTAGTGTCCAGGGAGTTCGCGGATGCGC
GCGAGAACAGGCCGACGCGCGCTCGGCCATGAACAAGCACAACAACGAGGGCGGGCC
GCACGACTATCCTGGACCACATGCACCTCAAATGCAAGTGCCACGGGCTGTCGGGCAG
CTGTGAGGTGAAGACCTGCTGGTGGGCGCAGCCTGACTTCCGTGCCATCGGTGACTTCC
TCAAGGACAAGTATGACAGCGCCTCGGAGATGGTAGTAGAGAAGCACCGTGAGTCCCG
AGGCTGGGTGGAGACCCTCCGGGCCAAGTACTCGCTCTTCAAGCCACCCACGGAGAGG
GACCTGGTCTACTACGAGAACTCCCCCACTTTTGTGAGCCCAACCCAGAGACGGGTT
CCTTTGGCACAAGGGACCGGACTTGCAATGTACCTCCACGGCATCGATGGCTGCGA
TCTGCTCTGCTGTGGCCGGGGCCACAACACGAGGACGGAGAAGCGGAAGGAAAAATG
CCACTGCATCTTCCACTGGTGCTGCTACGTCAGCTGCCAGGAGTGATTTCGCATCTACG
ACGTGCACACCTGCAAGTAGGGCACCAG

Figure 37

MEPHLLGLLLGLLLGGTRVLAGYPIWWSLALGQQYTSLSQPLLCGSIPGLVPKQLRFCRN
 YIEIMPSVAEGVKLGIQECQHQRGRRWNCTTIDDSLAIFGPVLDKATRESAFVHAIASAGV
 AFAVTRSCAEGTSTICGCDSHHKGPPGEGWKWGGCSEDADFGVLVSREFADARENRPDAR
 SAMNKHNNAGRTTILDHMHKCKCHGLSGSCEVKTCWWAQPFDRAIGDFLKDKEYDSAS
 EMVVEKHRESRGWVETLRAKYSLFKPPTERDLVYYENSPNFCEPNPETGSFGTRDRTCNVT
 SHGIDGCDLLCCGRGHNTRTEKRKEKCHCI

Figure 38

ATGAGTCCCCGCTCGTGCTGCGTTCGCTGCGCCTCCTCGTCTTCGCCGTCTTCTCAGCC
 GCCGCGAGCAACTGGCTGTACCTGGCCAAGCTGTCTCGTGGTGGGGAGCATCTCAGAGG
 AGGAGACGTGCGAGAACTCAAGGGCCTGATCCAGAGGCAGGTGCAGATGTGCAAGC
 GGAACCTGGAAGTCATGGACTCGGTGCGCCGCGGTGCCAGCTGGCCATTGAGGAGTG
 CCAGTACCAGTTCGGAACCGGCGCTGGAAGTGTCCACACTCGACTCCTTGCCCGTCT
 TCGGCAAGGTGGTGACGCAAGGGATTCTGGGAGGCGGCCTTGGTGTACGCCATCTCTTC
 GGCAGGTGTGGCCTTTGCAAGTACGCGGGCGTGCAGCAGTGGGGAGCTGGAGAAGTGC
 GGCTGTGACAGGACAGTGCATGGGGTCAGCCACAGGGCTTCCAGTGGTTCAGGATGCT
 CTGACAACATCGCCTACGGTGTGGCCTTCTCACAGTCGTTTGTGGATGTGCGGGAGAGA
 AGCAAGGGGGCCTCGTCCAGCAGAGCCCTCATGAACCTCCACAACAATGAGGCCGGCA
 GGAAGGCCATCCTGACACACATGCGGGTGGAAATGCAAGTGCCACGGGGTGTACGGCTC
 CTGTGAGGTAAAGACGTGCTGGCGAGCCGTGCCGCCCTTCCGCCAGGTGGGTACGCA
 CTGAAGGAGAAGTTTGTGGTGGCCACTGAGGTGGAGCCACGCCGCGTGGGCTCCTCCA
 GGGCACTGGTGCCACGCAACGCACAGTTCAAGCCGCACACAGATGAGGACTTGGTGTA
 CTTGGAGCCTAGCCCCGACTTCTGTGAGCAGGACATGCGCAGCGGCGTGCTGGGCACG
 AGGGGCCGACATGCAACAAGACGTCCAAGGCCATCGACGGCTGTGAGCTGCTGTGCT
 GTGGCCGCGGCTTCCACACGGCGCAGGTGGAGCTGGCTGAACGCTGCAGCTGCAAATT
 CCACTGGTGCTGCTTCGTCAAGTGCCGGCAGTGCCAGCGGCTCGTGGAGTTGCACACG
 TGCCGATGA

Figure39

MSPRSLRSLRLLVFAVFSAAAASNWLYLAKLSSVGSISEEETCEKLKGLIQRQVQMCKRNL
 EVMDSVRRGAQLAIEECQYQFRNRRWNCSTLDSLVPFGKVVTQGIRESAALVYAISSAGVA
 FAVTRACSSGELEKCGCDRTVHGVSPQGFQWSGSDNIAYGVAFSQSFDVRRERSKGASSS
 RALMNLHNNEAGRKAILTHMRVECKCHGVSGSCEVKTCWRAVPPFRQVGHALKEKFDG
 ATEVEPRRVGSSRALVPRNAQFKPHTDEDLVYLEPSPDFCEQDMRSGVLGTRGRTCNKTS
 KAIDGCELLCCGRGFHTAQVELAERCSCKFHWCCFVKCRQCQRLVELHTCR

Figure 40

ATTAATTCTGGCTCCACTTGTGCTCGGCCAGGTTGGGGAGAGGACGGAGGGTGGCC
 GCAGCGGGTTCCTGAGTGAATTACCCAGGAGGGACTGAGCACAGCACCAACTAGAGA
 GGGGTCAGGGGGTGCGGGACTCGAGCGAGCAGGAAGGAGGCAGCGCCTGGCACCAGG
 GCTTTGACTCAACAGAATTGAGACACGTTTGTAATCGCTGGCGTGCCCCGCGCACAGG
 ATCCCAGCGAAAATCAGATTTCTTGGTGAGGTTGCGTGGGTGGATTAATTTGAAAAA
 GAAACTGCCTATATCTTGCCATCAAAAACTCACGGAGGAGAAGCGCAGTCAATCAAC
 AGTAACTTAAGAGACCCCCGATGCTCCCCTGGTTTAACTTGTATGCTTGAAAATTATC
 TGAGAGGGAATAAACATCTTTTCTTCTTCCCTCTCCAGAAGTCCATTGGAATATTAAG
 CCCAGGAGTTGCTTTGGGGATGGCTGGAAGTGCAATGTCTTCCAAGTTCTTCTAGTGG

CTTTGGCCATATTTTTCTCCTTCGCCCAGGTTGTAATTGAAGCCAATTCTTGGTGGTTCG
TAGGTATGAATAACCCTGTTCAGATGTCAGAAGTATATATTATAGGAGCACAGCCTCTC
TGCAGCCAACTGGCAGGACTTTCTCAAGGACAGAAGAACTGTGCCACTTGTATCAGG
ACCACATGCAGTACATCGGAGAAGGCGCGAAGACAGGCATCAAAGAATGCCAGTATC
AATTCGACATCGACGGTGGAAGTGCAGCACTGTGGATAACACCTCTGTTTTTGGCAGG
GTGATGCAGATAGGCAGCCGCGAGACGGCCTTCACATACGCCGTGAGCGCAGCAGGG
GTGGTGAACGCCATGAGCCGGGCGTGCCGCGAGGGCGAGCTGTCCACCTGCGGCTGCA
GCCGCGCCGCGCGCCCCAAGGACCTGCCGCGGGAAGTGGCTCTGGGGCGGCTGCGGCGA
CAACATCGACTATGGCTACCGCTTTGCCAAGGAGTTCGTGGACGCCGCGAGCGGGAG
CGCATCCACGCCAAGGGCTCCTACGAGAGTGCTCGCATCCTCATGAACCTGCACAACA
ACGAGGCCGCGCCGCGAGGACGGTGTACAACCTGGCTGATGTGGCCTGCAAGTGCCATGG
GGTGTCCGGCTCATGTAGCCTGAAGACATGCTGGCTGCAGCTGGCAGACTTCCGCAAG
GTGGGTGATGCCCTGAAGGAGAAGTACGACAGCGCGGCGGCCATGCGGCTCAACAGC
CGGGGCAAGTTGGTACAGGTCAACAGCCGCTTCAACTCGCCACACACAAGACCTGG
TCTACATCGACCCCAGCCCTGACTACTGCGTGCGCAATGAGAGCACCGGCTCGCTGGG
CACGCAGGGCCGCTGTGCAACAAGACGTCGGAGGGCATGGATGGCTGCGAGCTCATG
TGCTGCGGCCGTGGGTACGACCAGTTCAAGACCGTGCAGACGGAGCGCTGCCACTGCA
AGTTCCACTGGTGCTGCTACGTCAAGTGCAAGAAGTGCACGGAGATCGTGGACCAGTT
TGTGTGCAAGTAGTGGGTGCCACCCAGCACTCAGCCCCGCTCCCAGGACCCGCTTATTT
ATAGAAAGTACAGTGATTCTGGTTTTTGGTTTTTATAGAAATATTTTTTATTTTTCCCAAG
AATTGCAACCGGAACCATTTTTTTTCTGTTACCATCTAAGAACTCTGTGGTTTTATTATT
AATATTATAATTATTATTATTGGCAATAATGGGGGTGGGAACCACGAAAAATATTTATTTT
GTGGATCTTTGAAAAGGTAATACAAGACTTCTTTTGGATAGTATAGAATGAAGGGGA
AATAACACATACCCTAACTTAGCTGTGTGGGACATGGTACACATCCAGAAGGTAAAGA
AATACATTTTCTTTTTCTCAAATATGCCATCATATGGGATGGGTAGGTTCCAGTTGAAA
GAGGGTGGTAGAAATCTATTCACAATTCAGCTTCTATGACCAAAATGAGTTGTAAATTC
TCTGGTGCAAGATAAAAGGTCTTGGGAAAACAAAACAAAACAAAACCTCCCTTC
CCCAGCAGGGCTGCTAGCTTGCTTTCTGCATTTTCAAATGATAATTTACAATGGAAGG
ACAAGAATGTCATATTCTCAAGGAAAAAAGGTATATCACATGTCTCATTCTCCTCAAAT
ATTCCATTTGCAGACAGACCGTCATATTCTAATAGCTCATGAAATTTGGGCAGCAGGGA
GGAAAGTCCCCAGAAATTAATAAAATTTAAACTCTTATGTCAAGATGTTGATTTGAAG
CTGTTATAAGAATTGGGATTCCAGATTTGTAAAAAGACCCCCAATGATTCTGGACACTA
GATTTTTTGTGGGGAGGTTGGCTTGAACATAAATGAAATATCCTGTATTTTCTTAGG
GATACTTGGTTAGTAAATTATAATAGTAGAAATAATACATGAATCCCATTCACAGGTTT
CTCAGCCCAAGCAACAAGGTAATTGCGTGCCATTACAGCACTGCACCAGAGCAGACAAC
CTATTTGAGGAAAAACAGTGAAATCCACCTTCTCTTCACTGAGCCCTCTCTGATTC
CTCCGTGTTGTGATGTGATGCTGGCCACGTTTCCAAACGGCAGCTCCACTGGGTCCCCT
TTGGTTGTAGGACAGGAAATGAAACATTAGGAGCTCTGCTTGGAAAACAGTTCACTAC
TTAGGGATTTTTGTTTCTTAAACTTTTATTTTGGAGGAGCAGTAGTTTTCTATGTTTTAA
TGACAGAACTTGGCTAATGGAATTCACAGAGGTGTTGCAGCGTATCACTGTTATGATCC
TGTGTTTAGATTATCCACTCATGCTTCTCCTATTGTACTGCAGGTGTACCTTAAACTGT
TCCCAGTGTACTTGAACAGTTGCATTTATAAGGGGGGAAATGTGGTTTAAATGGTGCCTG
ATATCTCAAAGTCTTTTGTACATAACATATATATATATACATATATATAAATATAAA
TATAAATATATCTCATTGCAGCCAGTGATTTAGATTTACAGCTTACTCTGGGGTTATCTC
TCTGTCTAGAGCATTGTTGTCCTTCACTGCAGTCCAGTTGGGATTATTCCAAAAGTTTTT
TGAGTCTTGAGCTTGGGCTGTGGCCCCGCTGTGATCATACCCTGAGCACGACGAAGCA
ACCTCGTTTCTGAGGAAGAAGCTTGAGTTCTGACTCACTGAAATGCGTGTTGGGTTGAA
GATATCTTTTTTCTTTTTCTGCCTCACCCCTTTGTCTCCAACCTCCATTTCTGTTCACTTT
GTGGAGAGGGCATTACTTGTTTCGTTATAGACATGGACGTTAAGAGATATTCAAACTC
AGAAGCATCAGCAATGTTTCTTTTTCTTAGTTTCTGTCAGAAATGGAAACCCATGCC
TATTAGAAATGACAGTACTTATTAATTGAGTCCCTAAGGAATATTAGCCCACTACATA
GATAGCTTTTTTTTTTTTTTTTTTTTTTTTAAATAAGGACACCTCTTCCAAACAGGCCATCA

AATATGTTCTTATCTCAGACTTACGTTGTTTTAAAAGTTTGGAAGATACACATCTTTTC
ATACCCCCCTTAGGAGGTTGGGCTTTCATATCACCTCAGCCAACTGTGGCTCTTAATT
TATTGCATAATGATATCCACATCAGCCAACTGTGGCTCTTTAATTTATTGCATAATGAT
ATTCACATCCCCTCAGTTGCAGTGAATTGTGAGCAAAAGATCTTGAAAGCAAAAAGCA
CTAATTAGTTTAAAATGTCACTTTTTTGGTTTTTATTATACAAAAACCATGAAGTACTTT
TTTTATTTGCTAAATCAGATTGTTCCTTTTTAGTGACTCATGTTTATGAAGAGAGTTGAG
TTTAACAATCCTAGCTTTTAAAAGAACTATTTAATGTAAAATATTCTACATGTCATTC
AGATATTATGTATATCTTCTAGCCTTTATTCTGTACTTTTAATGTACATATTTCTGTCTTG
CGTGATTTGTATATTTCACTGGTTTAAAAAACAAACATCGAAAGGCTTATTCCAAATGG
AAG

Figure 41

MAGSAMSSKFFLVALAIFFSFAQVVIEANSWWSLGMNPNVQMSEVYIIGAQPLCSQLAGLS
QGQKKLCHLYQDHMQYIGEGAKTGIKECQYQFRHRRWNCSTVDNTSVFGRVMQIGSRET
AFTYAVSAAGVVNAMSRACREGELSTCGCSRAARPKDLPRDWLWGGCGDNIDYGYRFA
KEFVDARERERIHAKGSYESARILMNLHNNEAGRRTVYNLADVACKCHGVSGSCSLKTC
WLQLADFRKVGDALKEKYDSAAAMRLNSRGKLVQVNSRFNSPTTQDLVYIDPSPDYCVR
NESTGSLGTQGRLCNKTSSEGMDGCELMCCGRGYDQFKTVQTERCHCKFHWCCYVKCKK
CTEIVDQFVCK

Figure 42

GGCACGAGCGCAGGAGACACAGGCGCTGGCTGCCCCGTCCGCTCTCCGCCTCCGCCGC
GCCCTCCTCGCCCGGGATGGGCCCCCCCCGCCGCCGCGGATCCCTCGCCTCCCGGCCGC
CGCCGTTGCGCTCGCCGCGCTCGCACTGAAGCCCGGGCCCTCGCGCGCCGCGGTTTCGC
CCCGCAGCCTCGCCCCCTGCCACCCGGGCGGCCGTAGGGCGGTCACGATGCTGCCGC
CCTTACCCTCCCGCCTCGGGCTGCTGCTGCTGCTGCTCCTGTGCCCGGCGCACGTCCGC
GGACTGTGGTGGGCTGTGGGCAGCCCCCTTGTTATGGACCCTACCAGCATCTGCAGGA
AGGCACGGCGGCTGGCCGGGCGGCAGGCCGAGTTGTGCCAGGCTGAGCCGGAAGTGG
TGGCAGAGCTAGCTCGGGGCGCCCCGGCTCGGGGTGCGAGAGTGCCAGTTCCAGTTCCG
CTTCCGCCGCTGGAATTGCTCCAGCCACAGCAAGGCCTTTGGACGCATCCTGCAACAG
GACATTCGGGAGACGGCCTTCGTGTTTCGCCATCACTGCGGCCGGCGCCAGCCACGCCG
TCACGCAGGCCTGTTCTATGGGCGAGCTGCTGCAGTGCGGCTGCCAGGCGCCCCGCGG
GCGGGCCCCCTCCCCGGCCCTCCGGCCTGCCCGGCACCCCCGGACCCCCTGGCCCCGCG
GGCTCCCCGGAAGGCAGCGCCGCCTGGGAGTGGGGAGGCTGCGGCGACGACGTGGAC
TTCGGGGACGAGAAAGTCGAGGCTCTTTATGGACGCGCGGCACAAGCGGGGACGCGGA
GACATCCGCGCGTTGGTGCAACTGCACAACAACGAGGCGGGCAGGCTGGCCGTGCGG
AGCCACACGCGCACCGAGTGCAAATGCCACGGGCTGTCGGGATCATGCGCGCTGCGCA
CCTGCTGGCAGAAGCTGCCTCCATTTTCGCGAGGTGGGCGCGCGGCTGCTGGAGCGCTT
CCACGGCGCCTCACGCGTCATGGGCACCAACGACGGCAAGGCCCTGCTGCCCGCCGTC
CGCACGCTCAAGCCGCGGGGCCGAGCGGACCTCCTCTACGCCGCCGATTGCCCCGACT
TTTGCGCCCCCAACCGACGCACCGGCTCCCCCGGCACGCGCGGTGCGGCCTGCAATAG
CAGCGCCCCGGACCTCAGCGGCTGCGACCTGCTGTGCTGCGGCCGCGGGCACCGCCAG

GAGAGCGTGCAGCTCGAAGAGAACTGCCTGTGCCGCTTCCACTGGTGCTGCGTAGTAC
AGTGCCACCGTTGCCGTGTGCGCAAGGAGCTCAGCCTCTGCCTGTGACCCGCCGCC
CGGCCGCTAGACTGACTTCGCGCAGCGGTGGCTCGCACCTGTGGGACCTCAGGGCACC
GGCACCGGGCGCCTCTCGCCGCTCGAGCCCAGCCTCTCCCTGCCAAAGCCCAACTCCC
AGGGCTCTGGAAATGGTGAGGCGAGGGGCTTGAGAGGAACGCCACCCACGAAGGCC
CAGGGCGCCAGACGGCCCCGAAAAGGCGCTCGGGGAGCGTTTAAAGGACACTGTACA
GGCCCTCCCTCCCCTTGGCCTCTAGGAGGAAACAGTTTTTTAGACTGGAAAAAAGCCA
GTCTAAAGGCCTCTGGATACTGGGCTCCCCAGAACTGCTGGCCACAGGATGGTGGGTG
AGGTTAGTATCAATAAAGATATTTAAACCAAAAAAAAAAAAAAAAAAAAAA

Figure 43

MLPPLPSRLGLLLLLLLCPAHVGGWVAVGSPLVMDPTSICRKARRLAGRQAELCQAEPE
VVAELARGARLGVRECQFQFRFRRWNCSSSHSKAFGRILQQDIRETAFVFAITAAGASHAVT
QACSMGELLQCGCQAPRGRAPRPSGLPGTPGPPGPAGSPEGSAAWEWGGCGDDVDFGD
EKSRLFMDARHKRGRGDIRALVQLHNNEAGRLAVRSHTRTECKCHGLSGSCALRTCWQK
LPPFREVGARLLERFHGASRVMGTNDGKALLPAVRTLKPPGRADLLYAADSPDFCAPNRR
TGSPGTRGRACNSSAPDLSGCDLLCCGRGHRQESVQLEENCLCRFWCCVQCHRCRVRK
ELSLCL

Figure 44

CACGCGTCCGGGCCAATCGGGACTATGAACCGGAAAGCGCTGCGCTGCCTGGGCCACC
TCTTTCTCAGCCTGGGCATGGTCTGCCTCCGGATCGGTGGCTTCTCCTCAGTGGTAGCTC
TGGGCGCAACGATCATCTGTAACAAGATCCCAGGCCTGGCTCCCAGACAGCGGGCGAT
CTGCCAGAGCCGGCCCGACGCCATCATCGTCATAGGAGAAGGCTCACAAATGGGCCTG
GACGAGTGTGAGTTTCAGTTCGCAATGGCCGCTGGAAGTGTCTGCACTGGGAGAGC
GCACCGTCTTCGGGAAGGAGCTCAAAGTGGGGAGCCGGGACGGTGCCTTACCTACGC
CATCATTGCCGCCGGCGTGGCCCACGCCATCACAGCTGCCTGTACCCATGGCAACCTG
AGCGACTGTGGCTGCGACAAAGAGAAGCAAGGCCAGTACCACCGGGACGAGGGCTGG
AAGTGGGGTGGCTGCTCTGCCGACATCCGCTACGGCATCGGCTTCGCCAAGGTCTTTGT
GGATGCCCGGGAGATCAAGCAGAATGCCCGGACTCTCATGAAGTGTGACAACAACGAG
GCAGGCCGAAAGATCCTGGAGGAGAACATGAAGCTGGAATGTAAGTGCCACGGCGTG
TCAGGCTCGTGCACCACCAAGACGTGCTGGACCACACTGCCACAGTTTCGGGAGCTGG
GCTACGTGCTCAAGGACAAGTACAACGAGGCCGTTACGTGGAGCCTGTGCGTGCCAG
CCGCAACAAGCGGCCACCTTCCTGAAGATCAAGAAGCCACTGTCGTACCGCAAGCCC
ATGGACACGGACCTGGTGTACATCGAGAAGTCGCCCACTACTGCGAGGAGGACCCGG
TGACCGGCAGTGTGGGCACCCAGGGCCGCGCCTGCAACAAGACGGCTCCCCAGGCCAG
CGGCTGTGACCTCATGTGCTGTGGGCGTGGCTACAACACCCACCAGTACGCCCGCGTG
TGGCAGTGCAACTGTAAGTTCCACTGGTGTGCTGCTATGTCAAGTGCAACACGTGCAGCG
AGCGCACGGAGATGTACACGTGCAAGTGAGCCCCGTGTGCACACCACCTCCCGCTGC
AAGTCAGATTGCTGGGAGGACTGGACCGTTTCCAAGCTGCGGGCTCCCTGGCAGGATG
CTGAGCTTGTCTTTTCTGCTGAGGAAGGTACTTTTCTGGGTTTCTGTCAGGCATCCGTG
GGGGAATAAATCTCTCAGAACCTCAACTATTCTGTTCCACACCCAATGCTGCTCCA
CCCTCCCCCAGACACAGCCCAAGTCCCTCCGCGGCTGGAGCGAAGCCTTCTGCAGCAG
GAACTCTGGACCCCTGGGCCTCATCACAGCAATATTTAACAATTTATTCTGATAAAAT
AATATTAATTTATTTAATTAATAAAGAATTCTTCCACCTCAAAAAAAAAAAAAAAAAA
AAAAAAAAAGGGGGG

Figure 45

MNRKARRCLGHLFLSLGMVYLRIGGFSSVVALGASII CNKIPGLAPRQRAICQSRPDAIIVIG
EGSQMGLDECQFQFRNGRWNC SALGERTVFGKELKVGSREAAFTYAIIAAGVAHAIT AAC
TQGNLSDCGCDKEKQGQYHRDEGWKWGGCSADIRY GIGFAKVFDAREIKQNARTLMNL
HNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEPV
RASRNKRPTFLKIKKPLSYRKPMDDLVYIEKSPNYCEEDPVTG SVGTQGRACNKTAPQAS
GCDLMCCGRGYNTHQYARVWQCNC FHWCCYVKCNTCSERTEMYTCK

Figure 46

MHRNFRKWIFYVFLCFGVLYVKLGALSSVVALGANIICNKIPGLAPRQRAICQSRPDAIIVIG
EGAQMGINECQYQFRFGRWNC SALGEKTVFGQELRVGSREAAFTYAIIAAGVAHAIT AA
CSQGNLSNCGCDREKQGYYNQAEGWKWGGCSADVRYGIDFSRRFVDAREIKKNARRLM
NLHNNEAGRKVLED RMQLECKCHGVSGSCTTKTCWTTLPKFREVGHLLKEKYNA AVQVE
VVRASRLRQPTFLRIKQLRSYQKPMETDLVYIEKSPNYCEEDAATG SVGTQGRLCNRTSPG
ADGCDTMCCGRGYNTHQYTKVWQCNC FHWCCFVKCNTCSERVEVFTCK

Figure 47

TCCGCTTACACACCAAGGAAAGTTGGGCTTTGAAGAATTCCATCCCCATGGCCACTGG
AGGAAGAATATTT CNCCCGTCTTGCTTACCCATCTCCCCAGTTTTTTTGGAAATTTTCTCTA
GCTGTTACTCCAGAGGATTATGTTTTCTTTCAAAGCCTTCTGTGTACATCTGTCTTTTTCAC
CTGTGTCCTCCA ACTCAGCCACAGCTGGTCCGGTGAACAATTTCTGATGACTGGTCCAA
AGGCTTACCTGATTTACTCCAGCAGTGTGGCAGCTGGTGCCCAGAGTGGTATTGAAGA
ATGCAAGTATCAGTTTGCCTGGGACCGCTGGA ACTGCCCTGAGAGAGCCCTGCAGCTG
TCCAGCCATGGTGGGCTTCGCAGTGCCAATCGGGAGACAGCATTTGTGCATGCCATCA
GTTCTGCTGGAGTCATGTACACCCTGACTAGAACTGCAGCCTTGGAGATTTTGATAAC
TGTGGCTGTGATGACTCCCGCAACGGGCAACTGGGGGGACAAGGCTGGCTGTGGGGAG
GCTGCAGTGACAATGTGGGCTTCGGAGAGGCGATTTCCAAGCAGTTTGTGCATGCCCT
GGAAACAGGACAGGATGCACGGGCAGCCATGAACCTGCACAACAACGAGGCTGGCCG
CAAGGCGGTGAAGGGCACCATGAAACGCACGTGTAAGTGCCATGGCGTGTCTGGCAGC
TGCACCACGCAGACCTGTTGGCTGCAGCTGCCCCGAGTTCCGCGAGGTGGGCGCGCACC
TGAAGGAGAAGTACCACGCAGCACTCAAGGTGGACCTGCTGCAGGGTGCTGGCAACA
GCGCGGCCGCCCCGCGGCCATCGCCGACACCTTTCTGCTCCATCTCTACCCGGGAGCTG
GTGCACCTGGAGGACTCCCCGGACTACTGCCTGGAGAACAAAACGCTAGGGCTGCTGG
GCACCGAAGGCCGAGAGTGCCTAAGGCGCGGGCGGGCCCTGGGTGCTGGGAACTCC
GCAGCTGCCGCGGCTCTGCGGGGACTGCGGGCTGGCGGTGGAGGAGCGCCGGGGCCG
AGACCGTGTCCAGCTGCAACTGCAAGTTCCACTGGTGCTGTGCAGTCCGCTGCGAGCA
GTGCCGCGGAGGGTCACCAAGTACTTCTGTAGCCGCGCAGAGCGGCCGCGGGGGGGG
GCTGCGCACAAACCCGGGAGAAAACCTAAGGGTTTCTCTGCCCCCTCCTTTTCCAC
TGGTTCTTGGCTTCCTTTAGAGACCCCGGTAATTGTGGAACCTAGGGAATGGGGAACCC
GCTCTCCAGACCTAGGGATCCTGAAAGGGAAAACTGCAATTTCTCCAAAGCTTGCC
ACTTTCCAGCCTGTTTCCCCAATTCCTCTGTGCTCTCCTAAAGCTCTGTCTGAATCCTCG
CAGCCACACCTAGGTCTGAAAACCTCAGGCTTTGAGTTACTGATCTTCCTTGGATTAGGA
AAACAGGTGTTCTCTCCCTCTCCTATCAGCCCTAATCTCTGACCTAGCCTATCAAC
CCTTAGGCGCTGGAAAAACCTTCTCATACACGCAGGACCCAGGTAACTCAAAGCTTT

GCCCTTTTGCCCACTGTCTGCTACCAGGGGCTCACCCCTCTGCTGCACCTCTCTTCTGCAC
AGCTCCTCCCCTGCTACTGCTGACCAAATTCAGGAATCTTGAATGCTTTCTCTCCTCT
TCTCCCTTTCCTTTCCTCAAAAAAACTGAGGAACTGGCCCCGGAAAAGCATGTCTTTG
GGGTTGGTTTCCTAGAGGCAGAGGTTGAAGATGGAAGAGGGAGCTCTGGAGTGCTAACT
TGAACACCAAGGGTGCTACTCATCCCTATGGTATCATATCATGAATGGACTTTACTAGT
GGGGCAATGACTTTCCTAGACAATAACCCGAGGGACTCCAGATACATACCCCGAAGGT
CTAGGAAATACGTTAAGGGCAGATTACAGTCATTTCTACCCCTTTAAAGGTAACCTTCTC
CCTTCTCCTGACCTACTTCCTCCTAGCAACCAACTTTACCTCTTCTTCTCCAAAGGATCT
TTGTTCTCTGAGCCAAGACTGAGGTAATAAAAGCCACTTTCCTCTTCAGATCCTGGTC
TGCACCTCTAGA

Figure 48

MFLSKPSVYICLFTCVLQLSHSWSVNNFLMTGPKAYLIYSSSVAAAGAQSGIEECKYQFAWD
RWNCPERALQLSSHGGLRSANREAFVHAISSAGVMYTLTRNCSLGDFFDNCGCCDDSRNGQ
LGGQGWLWGGCSDNVGFGEAISKQFVDALETGQDARAAMNLHNNEAGRKA VKGTMKR
TCKCHGVSGSCTTQTCWLQLPEFREVGAHLKEKYHAALKVDLLQGAGNSAAARGAIADT
FRSISTREL VHLEDSPDYCLNKTLGLLGTEGRECLRRGRALGRWELRSCRRLCGDCGLAV
EERRAETVSSCNCKFWCCAVRCEQCRRRVTKYFCSRAERPRGGAAHKPGRKP

Figure 49

GCGGCCGCGTCGACGGAGGGGCTGCAGCTCCGTGAGCCCGGCAGAGCCACCCTGAGCT
CGGTGAGAGCAAAGCCAGAGCCCCAGTCCTTTGCTCGCCGGCTTGCTATCTCTCTCGA
TCACTCCCTCCCTTCCTCCCTCCCTTCCTCCCGCGCGCCGCGCGCGCTGGGGAAGCG
GTGAAGAGGAGTGGCCCGGCCCTGGAAGAATGCGGCTCTGACAAGGGGACAGAACCC
AGCGCAGTCTCCCCACGGTTTAAGCAGCACTAGTGAAGCCAGGCAACCCAACCGTGC
CTGTCTCGGACCCCGCACCCAAACCACTGGAGGTCCTGATCGATCTGCCACCGGAGC
CTCCGGGCTTCGACATGCTGGAGGAGCCCCGGCCGCGGCCTCCGCCCTCGGGCCTCGC
GGGTCTCCTGTTCTGGCGTTGTGCAGTCGGGCTCTAAGCAATGAGATTCTGGGCCTGA
AGTTGCCTGGCGAGCCGCGCTGACGGCCAACACCGTGTGCTTGACGCTGTCCGGCCT
GAGCAAGCGGCAGCTAGACCTGTGCCTGCGCAACCCCGACGTGACGGCGTCCGCGCTT
CAGGGTCTGCACATCGCGGTCCACGAGTGTGAGCACCAGCTGCGCGACCAGCGCTGGA
ACTGCTCCGCGCTTGAGGGCGGCGGCCGCTGCCGCACCACAGCGCCATCCTCAAGCG
CGGTTTCCGAGAAAGTGCTTTTTCTTCTCCATGCTGGCTGCTGGGGTCATGCACGCAG
TAGCCACGGCCTGCAGCCTGGGCAAGCTGGTGAGCTGTGGCTGTGGCTGGAAGGGCAG
TGGTGAGCAGGATCGGCTGAGGGCCAACTGCTGCAGCTGCAGGCACTGTCCCGAGGC
AAGAGTTTCCCCCACTCTCTGCCCAGCCCTGGCCCTGGCTCAAGCCCCAGCCCTGGCCC
CCAGGACACATGGGAATGGGGTGGCTGTAACCATGACATGGACTTTGGAGAGAAGTTC
TCTCGGGATTCTTGATTCCAGGGAAGCTCCCCGGGACATCCAGGCACGAATGCGAA
TCCACAACAACAGGGTGGGGCGCCAGGTGGTAAGTGAACCTGAAGCGGAAATGCA
AGTGTGATGGCACATCAGGCAGCTGCCAGTTCAAGACATGCTGGAGGGCGGCCCCAGA
GTTCCGGGCAGTGGGGGCGGCGTTGAGGGAGCGGCTGGGCGGGGCCATCTTCATTGAT
ACCCACAACCGCAATTCTGGAGCCTTCCAGCCCCGTCTGCGTCCCCGTGCGCTCTCAGG
AGAGCTGGTCTACTTTGAGAAAGTCTCCTGACTTCTGTGAGCGAGACCCCACTATGGGCT
CCCCAGGGACAAGGGGGCGGGCCTGCAACAAGACCAGCCGCTGTTGGATGGCTGTGG
CAGCCTGTGCTGTGGCCGTGGGCACAACGTGCTCCGGCAGACACGAGTTGAGCGCTGC
CATTGCCGCTTCCACTGGTGCTGCTATGTGCTGTGTGATGAGTGCAAGGTTACAGAGTG
GGTGAATGTGTGTAAGTGAGGGTCAGCCTTACCTTGGGGCTGGGGAAGAGGACTGTGT
GAGAGGGGCGCCTTTTCAGCCCTTTGCTCTGATTTCTTCCAAGGTCACCTTTGGTCCCT

GGAAGCTTAAAGTATCTACCTGGAAACAGCTTTAGGGGTGGTGGGGGTCAGGTGGACT
CTGGGATGTGTAGCCTTCTCCCAACAATTGGAGGGTCTTGAGGGGAAGCTGCCACCC
CTCTTCTGCTCCTTAGACACCTGAATGGACTAAGATGAAATGCACTGTATTGCTCCTCC
CACTTCTCAACTCCAGAGCCCCCTTTAACCTGATTCATACTCCTTTTGGCTGGGGAGTC
CCTATAGTTTCACTACTCCTCTCCCTTGAGGGATAACCCAGGCACTGTTTGGAGCCAT
AAGATCTGTATCTAGAAAGAGATCACCACTCCTATGTACTATCCCCAACTCCTTTAC
TGCAGCCTGGGCTCCCTCTTGTGGGATAATGGGAGACAGTGGTAGAGAGGTTTTCTTG
GGAAAGAGACAGAGTGCTGAGGGGCACTCTCCCTGAATCCTCAGAGAGTTGTCTGTC
CAGGCCCTTAGGGAAAGTTGTCTCCTTCCATTCAGATGTTAATGGGGACCTCCAAAGGA
AGGGGTTTTCCCATGACTCTTGGAGCCTCTTTTTCTTCTTCAGCAGGAAGGGTGGGAA
GGGATAATTTATCATACTGAGACTTGTCTTGGTTCCTGTTTGAACTAAAATAAATTA
AGTTACTGGAAAAAAAAAAAAAAAAAAAAA

Figure 50

MLEEPRPRPPPSGLAGLLFLALCSRALSNEILGLKLPGEPLTANTVCLTSLGLSKRQLDLCL
RNPDVTASALQGLHIAVHECQHQLRDQRWNCSALEGGGRLPHHSAILKRGFRESAFSFSM
LAAGVMHAVATACSLGKLVSCGCGWKGSGEQDRLRAKLLQLQALSRGKSFPHSLPSPGP
GSSPSPGPQDTEWGGCNHDMDFGEKFSRDFLDSREAPRDIQARMRIHNNRVGRQVV TEN
LKRKCKCHGTSGSCQFKTCWRAAPEFRAVGAALRERLGRAIFIDTHNRNSGAFQPRLRPR
LSGELVYFEKSPDFCERDPTMGSPGTRGRACNKTSRLLDGCGSLCCGRGHNVLRQTRVER
CHCRFWCCYVLCDECKVTEWVNVCK

Figure 51

TAACCCGCGCCTCCGCTCTCCCCGGCTGCAGGCGGCGTGCAGGACCAGCGGCGGCCG
TGCAGGCGGAGGACTTCGGCGCGGCTCCTCCTGGGTGTGACCCCGGGCGCGCCCGCCG
CGCGACGATGAGGGCGCGGCCGCGAGGTCTGCGAGGCGCTGCTCTTCGCCCTGGCGCTC
CAGACCGGCGTGTGCTATGGCATCAAGTGGCTGGCGCTGTCCAAGACACCATCGGCCC
TGGCACTGAACCAGACGCAACACTGCAAGCAGCTGGAGGGTCTGGTGTCTGCACAGGT
GCAGCTGTGCCGCGAGCAACCTGGAGCTCATGCACACGGTGGTGCACGCCGCCCGCGAG
GTCATGAAGGCCTGTCGCCGGGCTTTGCCGACATGCGCTGGAAGTGTCTCCTCCATTGA
GCTCGCCCCCACTATTTGCTTGACCTGGAGAGAGGGACCCGGGAGTCGGCCTTCGTG
TATGCGCTGTCGCCGCCACCATCAGCCACGCCATCGCCCGGGCCTGCACCTCCGGCG
ACCTGCCCGGCTGCTCCTGCGGCCCGCTCCAGGTGAGCCACCCGGGCGCGGAACCG
CTGGGGAAGATGTGCGGACAACCTCAGCTACGGGCTCCTCATGGGGGCAAGTTTTCC
GATGCTCCTATGAAGGTGAAAAAACAGGATCCCAAGCCAATAAACTGATGCGTCTAC
ACAACAGTGAAGTGGGGAGACAGGCTCTGCGCGCCTCTCTGGAAATGAAGTGTAAGTG
CCATGGGGTGTCTGGCTCCTGCTCCATCCGCACCTGCTGGAAGGGGCTGCAGGAGCTG
CAGGATGTGGCTGCTGACCTCAAGACCCGATACTGTGCGCCACCAAGGTAGTGCACC
GACCCATGGGCACCCGCAAGCACCTGGTGCCCAAGGACCTGGATATCCGGCCTGTGAA
GACTGGGAACCTTGTTTATTTGCAGAGCTCACCTGACTTTTGCATGAAGAATGAGAAG
GTGGGCTCCCACGGGACACAAGACAGGCAGTGCAACAAGACTTCCAACGGAAGCGAC
AGCTGCGACCTTATGTGCTGCGGGCGTGGCTACAACCCCTACACAGACCGCGTGGTCG
AGCGGTGCCACTGTAAGTACCACTGGTGTGCTACGTCACCTGCCGAGGTGTGAGCGT
ACCGTGGAGCGCTATGTCTGCAAGTGAGGCCCTGCCCTCCGCCCCACGCAGGAGCGAG
GACTTTGCTCAAGGACCTCAGCAACTGGGGCCGGGGGCTGGAGACACTCCATGGAG
CTCTGCTTGTGAATTCCAGATGCCAGGCATGGGAGGCGGCTTGTGCTTTGCCTTCACTT
GGAAGCCACCAGGAACAGAAGGTCTGGCCACCTGGAAGGAGNGCAGGACATCAAAG
GAAACCGACAAGATTAAAAATAACTTGGCAGCCTGAGNTCTGGAGTGCCACAGNNTG

GTGTAAGGAGCGGGGCTTGGGATCGGTGAGACTGATACAGACTTGACCTTTCAGGGCC
ACAGAGACCAGCCTCCGGGAAGGGTCTGCCCGCCTTCTTCAGAATGTTCTGCGGGAC
CCCCTGGCCACCCCTGGGGTCTGAGCCTGCTGGGCCACCACATGGAATCACTAGCTTCG
GGTTGTAAATGTTTTCTTTGTTNTTGCTTTTTCTTCCTTTGGGATGTTGGAAGCTACA
GAAATATTTATAAAACATAGCTTTTTCTTTGGGGTGGCACTTCTCAATTCCTCTTTATAT
ATTTTANATATATAAATATATATGTATATATAATGATCTCTAATNTAAACTAGCTT
TTTAAGCAGCTGTATGAAATAAATGCTGAGTGAGCCCCAGCCCGCCCTGCAGTTCCC
GGCCTCGTCAAGTGAACCTCGGCAGACCCTGGGGCTGGCAGAGGGAGCTCTCCAGTTTC
CGGGCA

Figure 52

MRARPQVCEALLFALALQTGVCYGIKWLALSKTSPALALNQTQHCKQLEGLVSAQVQLCR
SNLELMHTTVVHAAREVMKACRRAFADMWRWNCSSIELAPNYLLDLERGTRESAFVYALSA
ATISHAIARACTSGDLPGCSCGPVPGEPGPGNRWGRCADNLSYGLLMGAKFSDAPMKVK
KTGSQANKLMRLHNSEVGRQALRASLEMKCKCHGVSGSCSIRTCWKGLQELQDVAADLK
TRYLSATKVVHRPMGTRKHLVPKDLDIRPKDWELVYLQSSPDFCMKNEKVGSHGTQDR
QCNKTSNGSDSCDLMCCGRGYNPYTDRVVERCHCKYHWCCYVTCRRCERTVERYVCK

Figure 53

GGCGCGCAAGATGCTGGATGGGTCCCCGCTGGCGCGCTGGCTGGCCGCGGCCCTTCGG
GCTGACGCTGCTGCTCGCCGCGCTGCGCCCTTCGGCCGCTACTTCGGGCTGACGGGCA
GCGAGCCCCTGACCATCCTCCCGCTGACCCTGGAGCCAGAGGCGGCCCGCCAGGCGCA
CTACAAGGCCTGCGACCGGCTGAAGCTGGAGCGGAAGCAGCGGCGCATGTGCGCGCG
GGACCCGGGCGTGGCAGAGACGCTGGTGGAGGCCGTGAGCATGAGTGCCTCGAGTG
CCAGTTCCAGTTCCGCTTTGAGCGCTGGAACCTGCACGCTGGAGGGCCGCTACCGGGCC
AGCCTGCTCAAGCGAGGCTTCAAGGAGACTGCCTTCCTCTATGCCATCTCCTCGGCTGG
CCTGACGCACGCACTGGCCAAGGCGTGCAGCGCGGGCCGCGCATGGAGCGCTGTACCTGC
GATGAGGCACCCGACCTGGAGAACCGTGAGGCCTGGCAGTGGGGGGCTGCGGAGAC
AACCTTAAGTACAGCAGCAAGTTCGTCAAGGAATTCCTGGGCAGACGGTCAAGCAAGG
ATCTGCGAGCCCGTGTGGACTTCCACAACAACCTCGTGGGTGTGAAGGTGATCAAGGC
TGGGGTGGAGACCACCTGCAAGTGCCACGGCGTGTGAGGCTCATGCACGGTGCGGACC
TGCTGGCGGCAGTTGGCGCCTTTCCATGAGGTGGGCAAGCATCTGAAGCACAAGTATG
AGACGGCACTCAAGGTGGGCAGCACCAACCAATGAAGCTGCCGGCGAGGCAGGTGCCA
TCTCCCCACCACGGGGCCGTGCCCTCGGGGGCAGGTGGCAGCGACCCGCTGCCCCGCAC
TCCAGAGCTGGTGCACCTGGATGACTCGCCTAGCTTCTGCCTGGCTGGCCGCTTCTCCC
CGGGCACCGCTGGCCGTAGGTGCCACCGTGAGAAGAACTGCGAGAGCATCTGCTGTGG
CCGCGGCCATAACACACAGAGCCGGGTGGTGACAAGGCCCTGCCAGTGCCAGGTGCGT
TGGTGTCTGCTATGTGGAGTGCAGGCAGTGCACGCAGCGTGAGGAGGTCTACACCTGCA
AGGGCTGAGTTCCCAGGCCCTGCCAGCCCTGCTGCACAGGGTGCAGGCATTGCACACG
GTGTGAAGGGTCTACACCTGCACAGGCTGAGTTCCTGGGCTCGACCAGCCCAGCTGCG
TGGGGTACAGGCATTGCACACAGTGTGAATGGGTCTACACCTGCATGGGCTGAGTCCC
TGGGCTCAGACCTAGCAGCGTGGGGTAGTCCCTGGGCTCAGTCCCTAGCTGCATGGGGT
GCAGGCATTGCACAGAGCATGAATGGGCCTACACCTGCCAAGGCTGAATCCCTGGGCC
CAGCCAGCCCTGCTGCACATGGCACAGGCATTGCACACGGTGTGAGGAGTGTACACCT
GCAAGGGCTGAGGCCCTGGGCCCAGTCAGCCCTGCTGCTCAGAGTGCAGGCATTGCAC
ATGGTGTGAGAAGGTCTACACCTGCAAGGGACGAGTCCCCGGGCGCTGGCCAACCCTGC
TGTGCAGGGTGAAGGGCCATGCATGCTAGTATGAGGGGTCTACACCTGCAAGGACTGAG
AGGCTTTT

Figure 54

MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPLTLEPEAAAQAHYKACDR
 LKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFKE
 TAFLYAIISSAGLTHALAKACSAGRMRCTCDEAPDLENREAWQWGGCGDNLKYSSKFVK
 EFLGRRSSKDLRARVDFHNNLVGVKVIKAGVETTCKCHGVSGSCTVRTCWRQLAPFHEVG
 KHLKHKYETALKVGSTTNEAAGEAGAISSPPRGRASGAGGSDPLRTPELVHLDSPSFCLA
 GRFSPGTAGRRCHREKNCESICCGRGHNTQSRVVTTRPCQCQVRWCCYVECRQCTQREEVY
 TCKG

Figure 55

AGCCTGCAAAAACCACAGAGGGCAAAGCCAGAAAGATGGAAAGGCACCCACCCATGC
 AGCTCACCACCTTGCCCTCAGGGAGACCCTCTTCACAGGGGCTTCTCAAAAGACCTCCCTA
 TGGTGGTTGGGCATTGCCTCCTTCGGGGTTCCAGAGAAGCTGGGCTGCGCCAATTTGCC
 GCTGAACAGCCGCCAGAAGGAGCTGTGCAAGAGGAAACCGTACCTGCTGCCGAGCAT
 CCGAGAGGGCGCCCGGCTGGGCATTGAGGAGTGCAGGAGCCAGTTCAGACACGAGAG
 ATGGAAGTGCATGATCACCGCCGCCGCCACTACCGCCCCGATGGGCGCCAGCCCCCTC
 TTTGGCTACGAGCTGAGCAGCGGCACCAAGAGACAGCATTTATTTATGCTGTGATGG
 CTGCAGGCCTGGTGCATTCTGTGACCAGGTCATGCAGTGCAGGCAACATGACAGAGTG
 TTCCTGTGACACCACCTTGACAGAACGGCGGCTCAGCAAGTGAAGGCTGGCACTGGGGG
 GGCTGCTCCGATGATGTCCAGTATGGCATGTGGTTCAGCAGAAAGTTCCTAGATTTCCC
 CATCGGAAACACCACGGGCAAAGAAAACAAAGTACTATTAGCAATGAACCTACATAA
 CAATGAAGCTGGAAGGCAGGCTGTGCGCAAGTTGATGTCAGTAGACTGCCGCTGCCAC
 GGAGTTTCCGGCTCCTGTGCTGTGAAAACATGCTGGAAAACCATGTCTTCTTTTGAAAA
 GATTGGCCATTTGTTGAAGGATAAATATGAAAACAGTATCCAGATATCAGACAAAATA
 AAGAGGAAAATGCGCAGGAGAGAAAAAGATCAGAGGAAAATACCAATCCATAAGGAT
 GATCTGCTCTATGTTAATAAGTCTCCCACTACTGTGTAGAAGATAAGAACTGGGAAT
 CCCAGGGACACAAGGCAGAGAATGCAACCGTACATCAGAGGGTGCAGATGGCTGCAA
 CCTCCTCTGCTGTGGCCGAGGTTACAACACCCATGTGGTCAGGCACGTGGAGAGGTGT
 GAGTGTAAGTTTCTGCTGCTGCTATGTCCGTTGCAGGAGGTGTGAAAGCATGACTG
 ATGTCCACACTTGCAAGTAACCACTCCATCCAGCCTTGGGCAAGATGCCTCAGCAATAT
 ACAATGGCATTGCAACCAGAGAGGTGCCCATCCCTGTGCAGCGCTAGTAAAGTTGACT
 CTTGCAGTGGAATCCC

Figure 56

MDRAALLGLARLCALWAALLVLPYGAQGNWMWLGIASFVPEKLGCANLPLNSRQKEL
 CKRKPYLLPSIREGARLGIQECGSQFRHERWNCMITAAATTAPMGASPLFGYELSSGTKET
 AFIYAVMAAGLVHVSVTRSCSAGNMTECSCDTTLQNGGSASEGWHWGGCSDDVQYGMWF
 SRKFLDFPIGNTTGKENKVLLAMNLHNNEAGRQAVAKLMSVDCRCHGVSGSCAVKTCWK
 TMSSFEEKIGHLLKDKYENSIQISDKTKRKMRRREKDQRKIPIHKDDLlyVNKSPNYCVEDK
 KLGIPTQGREGNRTSEGADGCNLLCCGRGYNTHVVRHVERCECKFIWCCYV
 RCRRCESMTDVHTCK

Figure 57

AGTTGAGGGATTGACACAAATGGTCAGGCGGGCGGCGGCGGAGAAGGAGGCGGAGGGCG
 CAGGGGGGAGCCGAGCCCGCTGGGCTGCGGAGAGTTGCGCTCTCTACGGGGCCGCGGC

CACTAGCGCGGCGCCGCCAGCCGGGAGCCAGCGAGCCGAGGGCCAGGAAGGCGGGAC
ACGACCCCGGCGCGCCCTAGCCACCCGGGTTCTCCCCGCCGCCGCGCTTCATGAATCG
CAAGTTTCCGCGGCGGCGGCGGCTGCGGTACGCAGAACAGGAGCCGGGGGAGCGGGC
CGAAAGCGGCTTGGGCTCGACGGAGGGCACCCGCGCAGAGGTCTCCCTGGCCGCAGG
GGGAGCCGCCGCCGGCCGTGCCCTGGCAGCCCCAGCGAGCGGCGCCAAGAGAGGA
GCCGAGAAAGTATGGCTGAGGAGGAGGCGCCTAAGAAAGTCCCGGGCCGCCGGCGGTG
GCGCGAGCTGGGAACTTTGTGCCGGGGCGCTCTCGGCCCGGCTGGCGGAGGAGGGCAG
CGGGGACGCCGGTGGCCGCCGCCGCCGCCAGTTGACCCCGGCGATTGGCGCGCCAG
CTGCTGCTGCTGCTTTGGCTGCTGGAGGCTCCGCTGCTGCTGGGGGTCCGGGCCAGGC
GGCGGGCCAGGGGCCAGGCCAGGGGCCCGGGCCGGGGCAGCAACCGCCGCCGCCGCC
TCAGCAGCAACAGAGCGGGCAGCAGTACAACGGCGAGCGGGGCATCTCCGTCCCGGA
CCACGGCTATTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCGTACAACCAG
ACCATCATGCCCAACCTGCTGGGCCACACGAACCAGGAGGACGCGGGCCTGGAGGTGC
ACCAGTTCTACCTCTAGTGAAAGTGCAGTGTTCCGCTGAGCTCAAGTTCTTCCTGTGC
TCCATGTACGCGCCCCGTGTGCACCGTGCTAGAGCAGGCGCTGCCGCCCTGCCGCTCCCT
GTGCGAGCGCGCGCGCCAGGGCTGCGAGGCGCTCATGAACAAGTTCGGCTTCCAGTGG
CCAGACACGCTCAAGTGTGAGAAGTTCCCGGTGCACGGCGCCGGCGAGCTGTGCGTGG
GCCAGAACACGTCCGACAAGGGCACCCCGACGCCCTCGCTGCTTCCAGAGTTCTGGAC
CAGCAACCCTCAGCACGGCGGGCGGAGGGCACCGTGGCGGCTTCCCGGGGGGCGCCGG
CGCGTCGGAGCGAGGCAAGTTCTCCTGCCCGCGCGCCCTCAAGGTGCCCTCCTACCTCA
ACTACCACTTCCTGGGGGAGAAGGACTGCGGCGCACCTTGTGAGCCGACCAAGGTGTA
TGGGCTCATGTACTTCGGGGCCGAGGAGCTGCGCTTCTCGCGCACCTGGATTGGCATT
GGTCAGTGCTGTGCTGCGCCTCCACGCTCTTCACGGTGCTTACGTACCTGGTGGACATG
CGGCGCTTCAGCTACCCGGAGCGGCCCATCATCTTCTTGTCCGGCTGTTACACGGCCGT
GGCCGTGGCCTACATCGCCGGCTTCCTCCTGGAAGACCGAGTGGTGTGTAATGACAAG
TTCGCCGAGGACGGGGCACGCACTGTGGCGCAGGGCACCAAGAAGGAGGGCTGCACC
ATCCTCTTCATGATGCTCTACTTCTTCAGCATGGCCAGCTCCATCTGGTGGGTGATCCTG
TCGCTCACCTGGTTCTTGGCGGCTGGCATGAAGTGGGGCCACGAGGGCCATCGAAGCCA
ACTCACAGTATTTTCACCTGGCCGCCTGGGCTGTGCCGGCCATCAAGACCATCACCATC
CTGGCGCTGGGCCAGGTGGACGGCGATGTGCTGAGCGGAGTGTGCTTCGTGGGGCTTA
ACAACGTGGACGCGCTGCGTGGCTTCGTGCTGGCGCCCCCTCTTCGTGTACCTGTTTATC
GGCACGTCTTTCTGCTGGCCGGCTTTGTGTGCTCTTCCGCATCCGCACCATCATGAA
GCACGATGGCACCAAGACCGAGAAGCTGGAGAAGCTCATGGTGCGCATTGGCGTCTTC
AGCGTGCTGTACACTGTGCCAGCCACCATCGTCATCGCCTGCTACTTCTACGAGCAGGC
CTTCCGGGACCAGTGGGAACGCAGCTGGGTGGCCCAGAGCTGCAAGAGCTACGCTATC
CCCTGCCCTCACCTCCAGGCGGGCGGAGGCGCCCCGCCGACCCGCCCATGAGCCCGG
ACTTCACGGTCTTCATGATTAAGTACCTTATGACGCTGATCGTGGGCATCACGTCGGGC
TTCTGGATCTGGTCCGGCAAGACCCTCAACTCCTGGAGGAAGTTCTACACGAGGCTCA
CCAACAGCAAACAAGGGGAGACTACAGTCTGAGACCCGGGGCTCAGCCCATGCCAG
GCCTCGGCCGGGGCGCAGCGATCCCCAAAGCCAGCGCCGTGGAGTTCGTGCCAATCC
TGACATCTCGAGGTTTCCTCACTAGACAACTCTCTTTCGCAGGCTCCTTTGAACAACTC
AGCTCCTGCAAAAGCTTCCGTCCCTGAGGCAAAAGGACACGAGGGCCCCGACTGCCAGA
GGGAGGATGGACAGACCTCTTGCCCTCACACTCTGGTACCAGGACTGTTGCTTTTATG
ATTGTAAATAGCCTGTGTAAGATTTTGTAAAGTATATTTGTATTTAAATGACGACCGAT
CACGCGTTTTTCTTTTCAAAAGTTTTTAATTATTTAGGGCGGTTTAACCATTTGAGGCT
TTTCTTCTTGCCCTTTTCGGAGTATTGCAAAGGAGCTAAAACTGGTGTGCAACCGCAC
AGCGCTCCTGGTCGTCCTCGCGCGCCTCTCCCTACCACGGGTGCTCGGGACGGCTGGGC
GCCAGCTCCGGGGCGAGTTCAGCACTGCGGGGTGCGACTAGGGCTGCGCTGCCAGGGT
CACTTCCCGCCTCCTCCTTTTGCCCCCTCCCCCTCCTTCTGTCCCCTCCTTTCTTTCCTG
GCTTGAGGTAGGGGCTCTTAAGGTACAGAACTCCACAAACCTTCCAAATCTGGAGGAG
GGCCCCCATACATTACAATTCTCCTTGCTCGGCGGTGGATTGCGAAGGCCCGTCCCT
TCGACTTCTGAAGCTGGATTTTAACTGTCCAGAACTTCTCCTCAACTTCATGGGGGC

CCACGGGTGTGGGCGCTGGCAGTCTCAGCCTCCCTCCACGGTCACCTTCAACGCCAG
 AACTCCCTTCTCCCACCTTAGTTGGTTACAGGGTGAGTGAGATAACCAATGCCAACT
 TTTTGAAGTCTAATTTTTGAGGGGTGAGCTCATTTTCATTCTCTAGTGTCTAAAACCTGGT
 ATGGGTTTGGCCAGCGTCATGGAAAGATGTGGTTACTGAGATTTGGGAAGAAGCATGA
 AGCTTTGTGTGGGTTGGAAGAGACTGAAGATATGGGTTATAAAAATGTTAATTCTAATTG
 CACACGGATGCCTGGCAACCTTGCCTTTGAGAATGAGACAGCCTGCGCTTAGATTTTAC
 CGGTCTGTAAAATGGAAATGTTGAGGTCACCTGGAAAGCTTTGTTAAGGAGTTGATGTT
 TGCTTTCCTTAACAAGACAGCAAAACGTAAACAGAAATTGAAAACCTGAAGGATATTT
 CAGTGTCATGGACTTCCTCAAAATGAAGTGCTATTTTCTTATTTTAAATCAAATAACTA
 GACATATATCAGAAACTTTAAAATGTAAAAGTTGTACACTTTCAACATTTTATTACGAT
 TATTATTCAGCAGCACATTCTGAGGGGGGAACAATTCACACCACCAATAATAACCTGG
 TAAGATTTTCAGGAGGTAAAGAAGGTGGAATAATTGACGGGGAGATAGCGCCTGAAAT
 AAACAAAATATGGGCATGCATGCTAAAGGGGAAAATGTGTGCAGGTCTACTGCATTAAA
 TCCTGTGTGCTCCTCTTTTGGATTTACAGAAATGTGTCAAATGTAAATCTTTCAAAGCC
 ATTTAAAAATATTCACTTTAGTTCTCTGTGAAGAAGAGGAGAAAAGCAATCCTCCTGAT
 TGTATTGTTTTAACTTTAAGAATTTATCAAAATGCCGGTACTTAGGACCTAAATTTAT
 CTATGTCTGTCATACGCTAAAATGATATTGGTCTTTGAATTTGGTATACATTTATTCTGT
 TCACTATCACAAAATCATCTATATTTATAGAGGAATAGAAGTTTATATATATATAATAC
 CATATTTTAAATTTACAAAATAAAAAATTCAAAGTTTTGTACAAAATTATATGGATTTT
 GTGCCTGAAAATAATAGAGCTTGAGCTGTCTGAACTATTTTACATTTTATGGTGTCTCA
 TAGCCAATCCCACAGTGTA AAAAATTCA

Figure 58

MAEEEAPKKSRAAGGGASWELCAGALSARLAEEGSGDAGGRRRPPVDPRLRLARQLLLL
 WLLEAPLLLGVRAQAAGQGPGQGPQPPPPQQQSGQQYNGERGIVPDHGYCQPI
 SIPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCTVL
 EQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHGAGELCVGQNTSDKGTPTP
 SLLPEFWTSNPQHGGGGHRRGGFPGGAGASERKGFSCPRALKVPSYLNHFLGEKDCGAPC
 EPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMRRFSYPERPIIFLSGCT
 AVAVAYIAGFLLEDREVVCNDKFAEDGARTVAQGTKKEGCTILFMMLYFFSMASIIWW
 VILSLTWFLAAGMKWGHEAIBANSQYFHLAAWAVPAIKTITILALGQVDGDVLSGVCFVG
 LNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKHDGKTEKLEKLMVRIGVFSV
 LYTVPATIVIACYFYEQA
 FRDQWERSWVAQSKSYAIPCPHLQAGGGAPPHPPMSPDFTVFMIKYLMTLIVGITSGFWI
 WSGKTLNSW RKFYTRLTNSKQGETTV

Figure 59

CGAGTAAAGTTTGCAAAGAGGCGCGGGAGGCGGCAGCCGCAGCGAGGAGGCGGCGGG
 GAAGAAGCGCAGTCTCCGGGTTGGGGGCGGGGGCGGGGGCGCCAAGGAGCCGGG
 TGGGGGGCGGCGGCCAGCATGCGGCCCGCAGCGCCCTGCCCCGCCTGCTGCTGCCGC
 TGCTGCTGCTGCCCGCCGCGGGCCGCGCCAGTTCCACGGGGAGAAGGGCATCTCCAT
 CCCGGACCACGGCTTCTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCCTACA
 ACCAGACCATCATGCCCAACCTTCTGGGCCACACGAACCAGGAGGACGCAGGCCTAGA
 GGTGCACCAAGTTCTATCCGCTGGTGAAGGTGCAGTGCTCGCCCCGAAGTGCCTTCTTCC
 TGTGCTCCATGTACGCACCCGTGTGCACCGTGCTGGAACAGGCCATCCCGCCGTGCCGC
 TCTATCTGTGAGCGCGCGCGCCAGGGCTGCGAAGCCCTCATGAACAAGTTCGGTTTTCA
 GTGGCCCGAGCGCCTGCGCTGCGAGCACTTCCCGCGCCACGGCGCCGAGCAGATCTGC
 GTCGGCCAGAACCCTCCGAGGACGGAGCTCCCGCGCTACTCACCACCGCGCCGCCGC

CGGGACTGCAGCCGGGTGCCGGGGGACACCCGGGTGGCCCCGGGCGGCGGCGGCGCTC
CCCCGCGCTACGCCACGCTGGAGCACCCCTTCCACTGCCCGCGCGTCTCAAGGTGCCA
TCCTATCTCAGCTACAAGTTTCTGGGCGAGCGTGATTGTGCTGCGCCCTGCGAACCTGC
GCGGCCCCGATGGTTCCATGTTCTTCTCACAGGAGGAGACGCGTTTCGCGCGCCTCTGGA
TCCTCACCTGGTTCGGTGCTGTGCTGCGCTTCCACCTTCTTCACTGTACACGTAAGTGG
TAGACATGCAGCGCTTCCGCTACCCAGAGCGGCCTATCATTTTTCTGTGCGGGCTGCTAC
ACCATGGTGTTCGGTGGCCTACATCGCGGGCTTCGTGCTCCAGGAGCGCGTGGTGTGCA
ACGAGCGCTTCTCCGAGGACGGTTACCGCACGGTGGTGCAGGGCACCAAGAAGGAGG
GCTGCACCATCCTCTTCATGATGCTCTACTTCTTCAGCATGGCCAGCTCCATCTGGTGG
GTCATCCTGTGCTCACCTGGTTCTTGGCAGCCGGCATGAAGTGGGGGCCACGAGGCCA
TCGAGGCCAACTCTCAGTACTTCCACCTGGCCGCCTGGGCGGTGCCGGCCGTCAAGAC
CATCACCATCCTGGCCATGGGCCAGATCGACGGCGACCTGCTGAGCGGCGTGTGCTTC
GTAGGCCTCAACAGCCTGGACCCGCTGCGGGGCTTCGTGCTAGCGCCGCTCTTCGTGTA
CCTGTTTCATCGGCACGTCCTTCTCTGGCCGGCTTCGTGCTGCTCTTCCGCATCCGCAC
CATCATGAAGCACGACGGCACCAAGACCGAAAAGCTGGAGCGGCTCATGGTGCAT
CGGCGTCTTCTCCGTGCTCTACACAGTGCCCGCCACCATCGTCATCGCTTGCTACTTCTA
CGAGCAGGCCTTCCGCGAGCACTGGGAGCGCTCGTGGGTGAGCCAGCACTGCAAGAGC
CTGGCCATCCCGTGCCCGGCGCACTACACGCCGCGCATGTCGCCCCGACTTCACGGTCTA
CATGATCAAATACCTCATGACGCTCATCGTGGGCATCACGTCGGGCTTCTGGATCTGGT
CGGGCAAGACGCTGCACTCGTGGAGGAAGTTCTACACTCGCCTACCAACAGCCGACA
CGGTGAGACCACCGTGTGAGGGACGCCCCAGGCCGGAACCGCGCGGCGCTTTCCTCC
GCCCCGGGTGGGGCCCCCTACAGACTCCGTATTTTATTTTTTAAATAAAAAACGATCGA
AACCATTTCATTTTAGGTTGCTTTTTAAAGAGAACTCTCTGCCCAACACCCCC

Figure 60

MRPRSALPRLLLPLLLLPAAGPAQFHGEKGISIPDHGFCQPISIPLCTDIAYNQTIMPNLLGHT
NQEDAGLEVHQFYPLVKVQCSPELRFLLCSMYAPVCTVLEQAIPPCRSICERARQGCALM
NKFGFQWPERLRCEHFPRHGAEQICVGQNHSEGDAPALLTAPPPGLQPGAGGTPGGPGG
GGAPPRYATLEHPFHCPRVLKVPSYLSYKFLGERDCAAPCEPARPDGSMFFSQEETRFARL
WILTWSVLCCASTFTVTYLVDMQRFYPERPIIFLSGCTMVSVAYIAGFVLQERVVCN
ERFSEDGYRTVVQGTKEGCTILFMMLYFFSMASIIWWVILSLTWFLAAGMKWGHEAIEA
NSQYFHLLAAWAVPAVKTTITLAMGQIDGDLISGVCFVGLNSLDPLRGFVLAPLFVYLFIGTS
FLLAGFVSLFRIRTIMKHDGKTEKLERLMVRIGVFSVLYTVPATIVIACYFYEQAFREHW
ERSWVSQHCKSLAIPCAHYTPRMSPDFTVYMIKYLMTLIVGITSGFVIWSGKTLHSWRKF
YTRLTNSRHGETTV

Figure 61

GCCGCTCCGGGTACCTGAGGGACGCGCGGCCCGCCCGCGGCAGGCGGTGCAGCCCCCCC
CCACCCCTTGGAGCCAGGCGCCGGGTCTGAGGATAGCATTTCTCAAGACCTGACTTA
TGGAGCACTTGTAACCTGAGATATTTCAAGTTGAAGGAAGAAATAGCTCTTCTCCTAAGA
TGGAATCTGTGGTTTGGGAATGTGGTTGATCAACTTGATATGTTGGCCAAATGTGCCCC
ATGTAATAAAATGAAAAGAAGAGACAAGATGATGTCATTTTCCCATATTGTGAAACCA
AAAACAAACGCCTTTTGTGAGACCAAGCTAACAAACCTCTGACGGTGCGAAGAGTATT
TAACTGTTTGAAGAATTTAACAGTAAGATACAGAAGAAGTACCTTCGAGCTGAGACCT
GCAGGTGTATAAATATCTAAAATACATATTGAATAGGCCTGATCATCTGAATCTCCTTC
AGACCCAGGAAGGATGGCTATGACTTGGATTGTCTTCTCTTTGGCCCTTGACTGTGT
TCATGGGGCATATAGGTGGGCACAGTTTGTCTTCTGTGAACCTATTACCTTGAGGATG
TGCCAAGATTTGCCTTATAATACTACCTTCATGCCTAATCTTCTGAATCATTATGACCAA
CAGACAGCAGCTTTGGCAATGGAGCCATTCCACCCTATGGTGAATCTGGATTGTTCTCG

GGATTTCCGGCCTTTTCTTTGTGCACTCTACGCTCCTATTTGTATGGAATATGGACGTGT
CACACTTCCCTGTCGTAGGCTGTGTCAGCGGGCTTACAGTGAGTGTTTGAAGCTCATGG
AGATGTTTGGTGTTCCTTGGCCTGAAGATATGGAATGCAGTAGGTTCCCAGATTGTGAT
GAGCCATATCCTCGACTTGTGGATCTGAATTTAGCTGGAGAACCAACTGAAGGAGCCC
CAGTGGCAGTGCAGAGAGACTATGGTTTTTGGTGTCCCCGAGAGTTAAAAATTGATCCT
GATCTGGGTATTCTTTTCTGCATGTGCGTGATTGTTTACCTCCTTGTCCAAATATGTAC
TTCAGAAGAGAAGAACTGTCATTTGCTCGCTATTTTCATAGGATTGATTTCAATCATTG
CCTCTCGGCCACATTGTTTACTTTTTTAACTTTTTTGATTGATGTCACAAGATTCCGTTA
TCCTGAAAGGCCTATTATATTTTATGCAGTCTGCTACATGATGGTATCCTTAATTTTCTT
CATTGGATTTTTGCTTGAAGATCGAGTAGCCTGCAATGCATCCATCCCTGCACAATATA
AGGCTTCCACAGTGACACAAGGATCTCATAATAAAGCCTGTACCATGCTTTTTATGATA
CTCTATTTTTTTACTATGGCTGGCAGTGTATGGTGGGTAATTCTTACCATCACATGGTTT
TTAGCAGCTGTGCCAAAGTGGGGTAGTGAAGCTATTGAGAAGAAAGCATTGCTGTTTCT
ACGCCAGTGCATGGGGCATCCCCGGAACCTCTAACCATCATCCTTTTAGCGATGAATAA
AATTGAAGGTGACAATATTAGTGGCGTGTGTTTTGTTGGCCTCTACGATGTTGATGCAT
TGAGATATTTTGTCTTGGCTCCCTCTGCCTGTATGTGGTAGTTGGGGTTTCTCTCCTCTT
AGCTGGCATTATATCCCTAAACAGAGTTCGAATTGAGATTCCATTAGAAAAGGAGAAC
CAAGATAAATTAGTGAAGTTTATGATCCGGATCGGTGTTTTTCAGCATTCTTTATCTCGT
ACCACTCTTGGTTGTAATTGGATGCTACTTTTATGAGCAAGCTTACCGGGGCATCTGGG
AAACAACGTGGATACAAGAAGCTGCAGAGAATATCACATTCCATGTCCATATCAGGT
TACTCAAATGAGTCGTCCAGACTTGATTCTCTTTCTGATGAAATACCTGATGGCTCTCA
TAGTTGGCATTCCCTCTGTATTTTGGGTTGGAAGCAAAAAGACATGCTTTGAATGGGCC
AGTTTTTTTCATGGTCGTAGGAAAAAAGAGATAGTGAATGAGAGCCGACAGGTACTCC
AGGAACCTGATTTTGTCTCAGTCTCTCCTGAGGGATCCAAATACTCCTATCATAAGAAAG
TCAAGGGGAACCTTCCACTCAAGGAACATCCACCCATGCTTCTTCAACTCAGCTGGCTAT
GGTGGATGATCAAAGAAGCAAAGCAGGAAGCATCCACAGCAAAGTGAGCAGCTACCA
CGGCAGCCTCCACAGATCACGTGATGGCAGGTACACGCCCTGCAGTTACAGAGGAATG
GAGGAGAGACTACCTCATGGCAGCATGTCACGACTAACAGATCACTCCAGGCATAGTA
GTTCTCATCGGCTCAATGAACAGTCACGACATAGCAGCATCAGAGATCTCAGTAATAA
TCCCATGACTCATATCACACATGGCACCAGCATGAATCGGGTTATTGAAGAAGATGGA
ACCAGTGCTTAATTTGTCTTGTCTAAGGTGGAAATCTTGTGCTGTTTAAAAAGCAGATT
TTATTCTTTGCCTTTTGCATGACTGATAGCTGTACTCACAGTTAACATGCTTTTCAAGTCAA
GTACAGATTGTGTCCACTGGAAAGGTAAATGATTGCTTTTTTTATATTGCATCAAACCTTG
GAACATCAAGGCATCCAAAACACTAAGAATTCTATCATCACAAAAATAATTCGTCTTTC
TAGGTTATGAAGAGATAATTATTTGTCTGGTAAGCATTTTTATAAACCCACTCATTTTAT
ATTTAGAAAAATCCTAAATGTGTGGTGACTGCTTTGTAGTGAACCTTTCATATACTATAA
ACTAGTTGTGAGATAACATTCTGGTAGCTCAGTTAATAAAACAATTTTCAGAATTAAAG
AAATTTTCTATGCAAGGTTTACTTCTCAGATGAACAGTAGGACTTTGTAGTTTTATTTC
ACTAAGTGAAAAAAGAACTGTGTTTTTAACTGTAGGAGAATTTAATAAATCAGCAAG
GGTATTTTAGCTAATAGAATAAAAGTGCAACAGAAGAATTGATTAGTCTATGAAAGG
TTCTCTTAAATTTCTATCGAAATAATCTTCATGCAGAGATATTCAGGGTTTGGATTAGC
AGTGGAATAAAGAGATGGGCATTGTTTCCCCTATAATTGTGCTGTTTTTATAACTTTTGT
AAATATTACTTTTTCTGGCTGTGTTTTTATAACTTATCCATATGCATGATGGAAAAATTT
TAATTTGTAGCCATCTTTTCCCATGTAATAGTATTGATTCATAGAGAACTTAATGTTCAA
AATTTGCTTTGTGGAGGCATGTAATAAGATAAACATCATACATTATAAGGTAACCACA
ATTACAAAATGGCAAAACA

Figure 62

MAMTWIVFSLWPLTVFMGHIGHSLFSCEPITLRMCQDLPYNTTFMPNLLNHYDQQTAAL
AMEPFHMPVNLDCSRDFRPFLCALYAPICMEYGRVTLPCRRLCQRAYSECSKLMEMFGVP

WPEDMECSRFPDCDEPYPRLVLDNLAGEPTEGAPVAVQRDYGFWCPRCLKIDPDLGYSFL
HVRDCSPPCPNMYFRREELSFARYFIGLISIICLSATLFTFLTFLIDVTRFRYPERPIIFYAVCY
MMVSLIFFIGFLEDREVACNASIPAQYKASTVTQGSNKACTMLFMILYFFTMAGSVWWVI
LTITWFLAAVPKWGWSEAIEKKALLFHASAWGIPGTLTILLAMNKEGDNISGVCVGLYDV
DALRYFVLAPLCLYVVVGVSLLLAGIISLNRVRIEIPLEKENQDKLVKFMIRIGVFSILYLVL
LVVIGCYFYEQAYRGIWETTWIQUERCHEYHPCPYQVTQMSRPDLILFLMKYLMALIVGIPS
VFWVGSKKTCFEWASFFHGRKKEIVNESRQVLQEPDFAQSLLRDPNTPHRSRGTSSTQGT
STHASSTQLAMVDDQRSKAGSIHSKVSSYHGSLHRSRDGRYTPCSYRGMEERLPHGSMR
LTDHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTS

Figure 63

GCTGCGCAGCGCTGGCTGCTGGCTGGCCTCGCGGAGACGCCGAACGGACGCGGCCGGC
GCCGGCTTGTGGGCTCGCCGCTGCAGCCATGACCCTCGCAGCCTGTCCCTCGGCCTCG
GCCCCGGACGTCTAAAATCCACACAGTCGCGCGCAGCTGCTGGAGAGCCGGCCGCTG
CCCCCTCGTCGCCGCATCACACTCCCGTCCCGGGAGCTGGGAGCAGCGCGGGCAGCCG
GCGCCCCCGTGCAAACCTGGGGGTGTCTGCCAGAGCAGCCCCAGCCGCTGCCGCTGCTA
CCCCCGATGCTGGCCATGGCCTGGCGGGGCGCAGGGCCGAGCGTCCCGGGGGCGCCCG
GGGGCGTCGGTCTCAGTCTGGGGTTGCTCCTGCAGTTGCTGCTGCTCCTGGGGCCGGCG
CGGGGCTTCGGGGACGAGGAAGAGCGGCGCTGCGACCCCATCCGCATCTCCATGTGCC
AGAACCTCGGCTACAACGTGACCAAGATGCCCAACCTGGTTGGGCACGAGCTGCAGAC
GGACGCCGAGCTGCAGCTGACAACCTTTCACACCGCTCATCCAGTACGGCTGCTCCAGC
CAGCTGCAGTTCTTCTTTGTTCTGTTTATGTGCCAATGTGCACAGAGAAGATCAACAT
CCCCATTGGCCCATGCGGCGGCATGTGTCTTTCAGTCAAGAGACGCTGTGAACCCGTC
TGAAGGAATTTGGATTTGCCTGGCCAGAGAGTCTGAACTGCAGCAAATTTCCACCACA
GAACGACCACAACCACATGTGCATGGAAGGGCCAGGTGATGAAGAGGTGCCCTTACCT
CACAAAACCCCCATCCAGCCTGGGGAAGAGTGTCACTCTGTGGGAACCAATTCTGATC
AGTACATCTGGGTGAAAAGGAGCCTGAACTGTGTGCTCAAGTGTGGCTATGATGCTGG
CTTATACAGCCGCTCAGCCAAGGAGTTCAGTATCTGGATGGCTGTGTGGGCCAGCC
TGTGTTTCATCTCCACTGCCTTCACAGTACTGACCTTCCTGATCGATTCTTCTAGGTTTT
CCTACCCTGAGCGCCCCATCATATTTCTCAGTATGTGCTATAATATTTATAGCATTGCTT
ATATTGTCAGGCTGACTGTAGGCCGGGAAAGGATATCCTGTGATTTTGAAGAGGCAGC
AGAACCTGTTCTCATCCAAGAAGGACTTAAGAACACAGGATGTGCAATAATTTTCTTGC
TGATGTACTTTTTTGGAAATGGCCAGCTCCATTTGGTGGGTATTCTGACACTCACTTGGT
TTTTGGCAGCAGGACTCAAATGGGGTCATGAAGCCATTGAAATGCACAGCTCTTATTT
CACATTGCAGCCTGGGCCATCCCCGAGTGAAAACCATTTGTCATCTTGATTATGAGACT
GGTGGATGCAGATGAACTGACTGGCTTGTGCTATGTTGGAAACCAAAAATCTCGATGCC
CTCACCGGGTTCGTGGTGGCTCCCTCTTACTTATTTGGTCATTGGAACTTTGTTCAAT
GCTGCAGGTTTGGTGGCCTTGTTCAAAATTCGGTCAAATCTTCAAAAGGATGGGACAA
AGACAGACAAGTTAGAAAGACTGATGGTCAAGATTGGGGTGTCTCAGTACTGTACAC
AGTTCTTGCAACGTGTGTGATTGCCTGTTATTTTTATGAAATCTCCAACCTGGGCACTTT
TCGGTATTCTGCAGATGATTTCAACATGGCTGTTGAAATGTTGAAAACCTTTATGTCTTT
GTTGGTGGGCATCACTTCAGGCATGTGGATTGGTCTGCCAAAAGTCTTCACACGTGGC
AGAAGTGTTCACACAGATTGGTGAATTCTGGAAAGGTAAAGAGAGAGAAGAGAGGAA
ATGTTTGGGTGAAGCCTGGAAAAGGCAGTGAGACTGTGGTATAAGGCTAGTCAGCCTC
CATGCTTTCTTCATTTTGAAGGGGGGAATGCCAGCATTTTGGAGGAAATTTACTAAAA
GTTTTATGCAGTGAATCTCAGTTTGAACAACTAGCAACAATTAAGTGACCCCCGTCAA
CCCCTGCCTCCCACCCCGACCCAGCATCAAAAACCAATGATTTTGCTGCAGACTTT
GGAATGATCCAAAATGGAAAAGCCAGTTAGAGGCTTTCAAAGCTGTGAAAAATCAAA
ACGTTGATCACTTTAGCAGGTTGCAGCTTGGAGCGTGGAGGTCCTGCCTAGATTCCAGG
AAGTCCAGGGCGATACTGTTTTCCCTGCAGGGTGGGATTGAGCTGTGAGTTGGTAAC
TAGCAGGGAGAAATATTAACCTTTTAAACCCTTTACCATTTTAAATACTAACTGGGTCT

TTCAGATAGCAAAGCAATCTATAAACACTGGAAACGCTGGGTTTCAGAAAAGTGTTACA
AGAGTTTTATAGTTTGGCTGATGTAACATAAACATCTTCTGTGGTGCGCTGTCTGCTGTT
TAGAACTTTGTGGACTGCACTCCCAAGAAGTGGTGTTAGAATCTTTCAGTGCCTTTGTC
ATAAAACAGTTATTTGAACAAACAAAAGTACTGTACTCACACACATAAGGTATCCAGT
GGATTTTTCTTCTGTCTTCTCTCTTAAATTTCAACATCTCTCTTCTTGGCTGCTGCTG
TTTTCTTCATTTTATGTTAATGACTCAAAAAAGGTATTTTTATAGAATTTTTGTACTGCA
GCATGCTTAAAGAGGGGAAAAGGAAGGGTGATTCACCTTCTGACAATCACTTAATTCA
GAGGAAAATGAGATTTACTAAGTTGACTTACCTGACGGACCCAGAGACCTATTGCAT
TGAGCAGTGGGGACTTAATATATTTTACTTGTGTGATTGCATCTATGCAGACGCCAGTC
TGGAAGAGCTGAAATGTTAAGTTTCTTGGCAACTTTGCATTACACACAGATTAGCTGTGT
AATTTTTGTGTGTCAATTACAATTAAAAGCACATTGTTGGACCATGACATAGTATACTC
AACTGACTTTAAACTATGGTCAACTTCAACTTGCATTCTCAGAATGATAGTGCCTTTA
AAATTTTTTTATTTTTTAAAGCATAAGAATGTTATCAGAATCTGGTCTACTTAGGACAA
TGGAGACTTTTTTCAGTTTTATAAAGGGAAGTGGAGACAGCTAATCCAAGTACTTGGTGC
TGTAATTGTTTCTAGTAATTGGCAAAGGCTCCTTGTAAGATTTCACTGGAGGCAGTGT
GGCCTGGAGTATTTATATGGTGCTTAATGAATCTCCAGAATGCCAGCCAGAAGCCTGAT
TGGTTAGTAGGGAATAAAGTGTAGACCATATGAAATGAACTGCAAAGTCTAATAGCCC
AGGTCTTAATTGCCTTTAGCAGAGGTATCCAAAGCTTTTAAAATTTATGCATACGTTCT
TCACAAGGGGGTACCCCGAGCAGCCTCTCGAAAATTGCACTTCTCTTAAAGTGTAACT
GGCCTTTCTCTTACCTTGCCTTAGGCCTTCTAATCATGAGATCTTGGGGACAAATTGACT
ATGTCACAGGTTGCTCTCCTTGTAACCTCATACCTGTCTGCTTCAGCAACTGCTTTGCAAT
GACATTTATTTATTAATTCATGCCTTAAAAAATAGGAAGGGAAGCTTTTTTTTTCTTT
TTTTTTTTTTCAATCACACTTTGTGGAAAAACATTTCCAGGGACTCAAAATTCCAAAAA
GGTGGTCAAATTCTGGAAGTAAGCATTTCCTCTTTTTTAAAAATTTGGTTTGAGCCTTAT
GCCCATAGTTTGACATTTCCCTTTCTTCTTTCTTTTGTTTTTGTGTGGTTCTTGAGCTC
TCTGACATCAAGATGCATGTAAAGTCGATTGTATGTTTTGAAGGCAAAGTCTTGGCTTT
TGAGACTGAAGTTAAGTGGGCACAGGTGGCCCTGCTGCTGTGCCAGTCTGAGTACC
TTGGCTAGACTCTAGGTCAGGCTCCAGGAGCATGAGAATTGATCCCCAGAAGAACCAT
TTAACTCCATCTGATACTCCATTGCCTATGAAATGTAAAATGTGAAGTCCCTGTGCTG
CTTGTAGACAGTTCCCATAACTGTCCACGGCCCTGGAGCACGCACCCAGGGGCAGAGC
CTGCCCTTACTCACGCTCTGCTCTGGTGTCTTGGGAGTTGTGCAGGGACTCTGGCCAG
GCAGGGGAAGGAAGACCAGGCGGTAGGGGACTGGTCTTGCTGTTAGAGTATAGAGGTT
TGTAATGCAGTTTTCTTCATAATGTGTGAGTGATTGTGTGACCAAGGCAGCATCTAGCA
GAAAGCCAGGCATGGAGTAGGTGATCGATACTTGTCAATGACTAAATAATAACAATAA
AAGAGCACTTGGGTGAATCTGGGCACCTGATTTCTGAGTTTGTAGTTCTGGAGCTAGTG
TTTTGACAATGCTTTGGGTTTTGACATGCCTTTTCCACAAATCTCTTGCCTTTTCAGGGC
AAAGTGTATTTGATCAGAAGTGGCCATTTGGATTAGTAGCCTTAGCAATGCTACAGGGT
TATAGGCCCTCTCCCTTTCACATTCCAGACAATGGAGAGTGTTTATGGTTTCAGGAAA
AGAAGTTGTGGCTGAGGGGTGAGTTACAGTGACCTTCAATCAACTCCATCACTTCTT
AAATCGGTATTTGTTAAAAAATCAGTTATTTTATTGAGTGCCGACTGTAGTAAA
GCCCTGAAATAGATAATCTCTGTTCTTCTAACTGATCTAGGATGGGGACGCACCCAGGT
CTGCTGAAGTTTACTGTTCTCTGGAAGGAGCAGGGACCTCTGGAATTCCCCTCTGT
TTCACTGTCTCCATTCCATAAATCTCTTCTGTGTGAGCCACCACACCCAGCCTGGGTCT
CTCTACTTTTAAACACATCTCTCATCCCTTTCCAGGACTTCCCTTCCAAGTCAGTTACAGG
TGGTTTTAACAGAAAGCATCAGCTCTGCTTCGTGACAGTCTCTGGAGAAATCCCTTAGG
AAGACTATGAGAGTAGGCCACAAGGACATGGGCCCACACATCTGCTTTGGCTTTGCCG
GCAATTCAGGGCTTGGGGTATTCCATGTGACTTGTATAGGTATATTTGAGGACAGCATC
TTGCTAGAGAAAAGGTGAGGGTTGTTTTCTTTCTCTGAAACCTACAGTAAATGGGTAT
GATTGTAGCTTCTCAGAAATCCCTTGGCCTCCAGAGATTAAACATGGTGCAATGGCAC
CTCTGTCCAACCTCCTTTCTGGTAGATTCTTTCTCTGCTTCATATAGGCCAAACCTCA
GGGCAAGGGAACATGGGGGTAGAGTGGTGCTGGCCAGAACCATCTGCTTGAGCTACTT
GGTTGATTCATATCCTCTTTCTTTTATGGAGACCCATTTCTCTGATCTCTGAGACTGTTGC

TGAAGTGGCAACTTACTTGGGCCTGAAACTGGAGAAGGGGTGACATTTTTTTAATTTCA
 GAGATGCTTTCTGATTTTCCTCTCCCAGGTCACCTGTCTCACCTGCACTCTCCAAACTCAG
 GTTCCGGGAAGCTTGTGTGTCTAGATACTGAATTGAGATTCTGTTTCAGCACCTTTTAGC
 TCTATACTCTCTGGCTCCCCTCATCCTCATGGTCACTGAATTAAATGCTTATTGTATTGA
 GAACCAAGATGGGACCTGAGGACACAAAGATGAGCTCAACAGTCTCAGCCCTAGAGG
 AATAGACTCAGGGATTTACCCAGGTCGGTGCAGTATTTGATTTCTGGTGAGGTGACCAC
 AGCTGCAGTTAGGAAGGGAGCCATTGAGCACAGACTTTGGAAGGAACCTTTTTTTTGT
 GTTTGTTTGTGTTGTTTGTGTTGTTTGTGTTGAGACAGGGTCTTGCTCTGCTACCCAGG
 CTGGGGCGCAATGGCACGATCTTGGCTCACTGCAACCTCTGCCTCCTGGGTTCAAGTGA
 TTCTCCTGCCACAGCCTCCTGAGGAGCTGGGACTACAGGTGCGTGCTACCACGCCCAG
 CTACTTCTGTATTTTTAGTAGAGACGGGGTTTCACTGTGTTGGCCAGGCTGGTCTCGAA
 CTCCTGACCTCATGATCTGCCCGCCTCAGCCTCCCAAAGTGCTGGGATTACAAGTGTGA
 GCCACCACACCTGGCCTGGAAGGAACCTCTTAAAATCAGTTTACGTCTTGATTTTGT
 CTGTGATGGAGGACACTGGAGAGAGTTGCTATTCCAGTCAATCATGTCGAGTCACTGG
 ACTCTGAAAATCCTATTGGTTCCTTTATTTTATTTGAGTTTAGAGTTCCTTCTGGGTTT
 GTATTATGTCTGGCAAATGACCTGGGTTATCACTTTTCTCCAGGGTTAGATCATAGAT
 CTTGGAAACTCCTTAGAGAGCATTGCTCCTACCAAGGATCAGATACTGGAGCCCCAC
 ATAATAGATTTCACTTCACTCTAGCCTACATAGAGCTTTCTGTTGCTGTCTCTTGCCATG
 CACTTGTGCGGTGATTACACACTTGACAGTACCAGGAGACAAATGACTTACAGATCCC
 CCGACATGCCTCTTCCCCTTGGCAAGCTCAGTTGCCCTGATAGTAGCATGTTTCTGTTTC
 TGATGTACCTTTTTTCTCTTCTTTGCATCAGCCAATTCCCAGAATTTCCCAGGCAA
 TTTGTAGAGGACCTTTTTTGGGGTCTATATGAGCCATGTCCTCAAAGCTTTTAAACCTC
 CTTGCTCTCCTACAATATTCAGTACATGACCACTGTCATCCTAGAAGGCTTCTGAAAAG
 AGGGGCAAGAGCCACTCTGCGCCACAAAGGTTGGATCCATCTTCTCTCCGAGGTTGTG
 AAAGTTTTCAAATTGTAATAAGGCTGGGGCCCTGACTTGGCTGTGGGCTTTGGGAGG
 GGTAAGCTGCTTTCTAGATCTCTCCAGTGAGGCATGGAGGTGTTTCTGAATTTTGTCT
 ACCTCACAGGGATGTTGTGAGGCTTGAAAAGGTCAAAAATGATGGCCCCCTGAGCTC
 TTTGTAAGAAAGGTAGATGAAATATCGGATGTAATCTGAAAAAAAGATAAAATGTGAC
 TTCCCCTGCTCTGTGCAGCAGTCGGGCTGGATGCTCTGTGGCNTTCTTGGGTCCTCATG
 CCACCCACAGCTCCAGGAACCTTGAAGCCAATCTGGGGACTTTCAGATGTTTGACAA
 AGAGGTACCAGGCAAACCTTCTGCTACACATGCCCTGAATGAATTGCTAAATTTCAA
 GGAAATGGACCCTGCTTTTAAGGATGTACAAAAGTATGTCTGCATCGATGTCTGTACTG
 TAAATTTCTAATTTATCACTGTACAAAGAAAACCCCTTGCTATTTAATTTTGTATTAAAG
 GAAAATAAAGTTTTGTTTGTAAAAA

Figure 64

MAWRGAGPSVPGAPGGVGLSLGLLLQLLLLLGPARGFGDEEERRCDPIRISM CQN LGYNV
 TKMPNLVGHELQTD AELQLTFTPLIQYGCSSQLQFFLCSVYVPMCTE KINIPGPGGMCL
 SVKRRCEPVLKEFGFAWPESLNC SKFPQNDHNHMCMEGPGDEEVPLPHKTPIQPGECHS
 VGTNSDQYIWVKRSLN CVLKCGYDAGLYSRSAKEFTDIWMAVWASLCFISTAFTVLTFID
 SSRFSYPERPIIFLSMCYNTISLAIYIVRLTVGRERISCD FEEA AEPVLIQEGLKNTGCAIIFLLM
 YFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKTIVILIMRLVDA
 DELTGLCYVGNQNL DALTG FVVAPLFTYLVIGTLFIAAGLVALFKIRSNLQKDGTKTDKLE
 RLMVKIGVFSVLYTVPATCVIACYFYEISNWALFRYSADDSNMAVEMLKTFMSLLVGIT
 SGMWIWSAKSLHTWQKCSNRLVNSGKVKREKRGNGWVKPGKGSETVV

Figure 65

ACCCAGGGACGGAGGACCCAGGCTGGCTTGGGGACTGTCTGCTCTTCTCGGCGGGAGC
CGTGGAGAGTCCTTTCCCTGGAATCCGAGCCCTAACCGTCTCTCCCCAGCCCTATCCGG
CGAGGAGCGGAGCGCTGCCAGCGGAGGCAGCGCCTTCCCGAAGCAGTTTATCTTTGGA
CGGTTTTCTTTAAAGGAAAAACGAACCAACAGGTTGCCAGCCCCGGCGCCACACACGA
GACGCCGGAGGGAGAAGCCCCGGCCCGGATTCTCTGCCTGTGTGCGTCCCTCGCGGG
CTGCTGGAGGCGAGGGGAGGGAGGGGGCGATGGCTCGGCCTGACCCATCCGCGCCGC
CCTCGCTGTTGCTGCTGCTCCTGGCGCAGCTGGTGGGCGGGGCGGCCGCCGCGTCCAA
GGCCCCGGTGTGCCAGGAAATCACGGTGCCCATGTGCCGCGGCATCGGCTACAACCTG
ACGCACATGCCCAACCAAGTTCAACCACGACACGCAGGACGAGGCGGGCCTGGAGGTG
CACCAGTTCTGGCCGCTGGTGGAGATCCAATGCTCGCCGGACCTGCGCTTCTTCCCTATG
CACTATGTACACGCCCATCTGTCTGCCCCGACTACCACAAGCCGCTGCCGCCCTGCCGCT
CGGTGTGCGAGCGCGCCAAGGCCGGCTGCTCGCCGCTGATGCGCCAGTACGGCTTCGC
CTGGCCCCGAGCGCATGAGCTGCGACCGCCTCCCGGTGCTGGGCGCGACGCCGAGGTC
CTCTGCATGGATTACAACCGCAGCGAGGCCACCACGGCGCCCCCAGGCCTTTCCCAG
CCAAGCCCACCTTCCAGGCCCGCCAGGGGCGCCGGCCTCGGGGGGCGAATGCCCCGC
TGGGGGCCCCGTTCTGTGTGCAAGTGTGCGGAGCCCTTCGTGCCATTCTGAAGGAGTCAC
ACCCGCTCTACAACAAGGTGCGGACGGGCCAGGTGCCCAACTGCGCGGTACCCTGCTA
CCAGCCGTCCTTCAGTGCCGACGAGCGCACGTTCCGCCACCTTCTGGATAGGCCTGTGGT
CGGTGCTGTGCTTCATCTCCACGTCCACCACAGTGGCCACCTTCCTCATCGACATGGAC
ACGTTCCGCTATCCTGAGCGCCCCATCATCTTCCTGTCAGCCTGCTACCTGTGCGTGTG
GCTGGGCTTCCTGGTGCCTGCTGGTGGGCCATGCCAGCGTGGCCTGCAGCCGCGAG
CACAACCACATCCACTACGAGACCACGGGCCCTGCACTGTGCACCATCGTCTTCCTCCT
GGTCTACTTCTTCGGCATGGCCAGCTCCATCTGGTGGGTCATCCTGTCGCTCACCTGGTT
CCTGGCCGCGCGATGAAGTGGGGCAACGAGGCCATCGCGGGCTACGGCCAGTACTTC
CACCTGGCTGCGTGGCTCATCCCCAGCGTCAAGTCCATCACGGCACTGGCGCTGAGCTC
CGTGGACGGGGACCCAGTGGCCGGCATCTGCTACGTGGGCAACCAGAACCTGAACTCG
CTGCGGGCGCTTCGTGCTGGGCCCCGCTGGTGTCTACCTGCTGGTGGGCACGCTCTTCCT
GCTGGCGGGCTTCGTGTGCTCTTCGCGCATCCGCAGCGTCATCAAGCAGGGCGGCACC
AAGACGGACAAGCTGGAGAAGCTCATGATCCGCATCGGCATCTTCACGCTGCTCTACA
CGGTCCCCGCCAGCATTGTGGTGGCCTGCTACCTGTACGAGCAGCACTACCGCGAGAG
CTGGGAGGGCGGCGCTACCTGCGCCTGCCCGGGCCACGACACCGGCCAGCCGCGCGCC
AAGCCCGAGTACTGGGTGCTCATGCTCAAGTACTTCATGTGCCTGGTGGTGGGCATCAC
GTCGGGCGTCTGGATCTGGTCCGGCAAGACGGTGGAGTCGTGGCGGCGTTTCACCAGC
CGCTGCTGCTGCCGCCCGCGGCGCGGCCACAAGAGCGGGGGCGCCATGGCCGCGAGGG
GACTACCCCGAGGCGAGCGCCGCGCTCACAGGCAGGACCGGGCCGCGGGGCCCGCC
GCCACCTACCACAAGCAGGTGTCCCTGTGCGACGTGTAGGAGGCTGCCGCCGAGGGAC
TCGGCCGAGAGCTGAGGGGAGGGGGGCGTTTTGTTGGTAGTTTTGCCAAGGTCACCT
TCCGTTTACCTTCATGGTGTGTTGCCCCCTCCCGCGGCGACTTGAGAGAGAGGGAAGAG
GGGCGTTTTGAGGAAGAACCTGTCCAGGTCTTCTCCAAGGGGCCAGCTCACGTGT
ATTCTATTTTGCCTTTCTTACCTGCCTTCTTATGGGAACCCTCTTTTAAATTTATATGTA
T

Figure 66

MARPDPSAPPSLLLLLLAQLVGRAAAASKAPVCQEITVPMCRGIGYNLTHMPNQFNHDTQ
 DEAGLEVHQFWPLVEIQSPDLRFFLCTMYTPICLPDYHKPLPPCRSV CERAKAGCSPLMR
 QYGFAPWPERMSCDRLPVLGRDAEVL CMDYNRSEATTAPPRPFPKPTLP GPPGAPASGGE
 CPAGGPFVCKCREPFVPILKESHPLYNKVRTGQVPNC AVPCYQPSFSADERTFATFWIGLW
 SVLCFISTSTTVATFLIDMDTF RYPERPIIFLSACYLCVSLGFLVRLVVGHASVACSREHNHIIH
 YETTG PALCTIVFLLVYFFGMASSIWWVILSLTWFLAAAMKWGNEAIAGYGQYFH LAAWL
 IPSVKSITALALSSVDGDPVAGICYVGNQNLNSLR RFVLGPLVLYLLVGT LFLLAGFVSLFRI
 RSVIKQGGTKTDKLEKLMIRIGIFTLLYTPASIVVACYLYEQHYRESWEAALTCACPGHD
 TGQPRAKPEYWVLM LKYFMCLVVGITSGVWIWSGKTVESWRRFTSRCCCRPRRGHKSGG
 AMAAGDYPEASAALTGRTGPPGPAATYHKQVSLSHV

Figure 67

GCAGCTCCAGTCCCGGACGCAACCCCGGAGCCGTCTCAGGTCCCTGGGGGGAACGGTG
 GGTTAGACGGGGACGGGAAGGGACAGCGGCCTTCGACCGCCCCCGAGTAATTGACCC
 AGGACTCATTTTCAGGAAAGCCTGAAAATGAGTAAAATAGTGAAATGAGGAATTTGAA
 CATTTTATCTTTGGATGGGGATCTTCTGAGGATGCAAAGAGTGATT CATCCAAGCCATG
 TGGTAAAATCAGGAATTTGAAGAAAATGGAGATGTTTACATTTTGT TGACGTGTATTT
 TTCTACCCCTCCTAAGAGGGCACAGTCTCTTCACCTGTGAACCAATTACTGTTCCCAGA
 TGTATGAAAATGGCCTACAACATGACGTTTTTCCCTAATCTGATGGGT CATTATGACCA
 GAGTATTGCCGCGGTGGAAATGGAGCATTTTCTTCCTCTCGCAAATCTGGAATGTTTAC
 CAAACATTGAAACTTTCTCTGCAAAGCATTTGTACCAACCTGCATAGAACAAATTCAT
 GTGGTTCCACCTTGTGCTAAACTTTGTGAGAAAGTATATTCTGATTGCAAAAAATTAAT
 TGACACTTTTGGGATCCGATGGCCTGAGGAGCTTGAATGTGACAGATTACAATACTGTG
 ATGAGACTGTTCTGTAACTTTTGATCCACACACAGAATTTCTTGGTCTCAGAAAGAAA
 ACAGAACAAAGTCCAAAGAGACATTGGATTTTGGTGTCCAAGGCATCTTAAGACTTCTG
 GGGGACAAGGATATAAGTTTCTGGGAATTGACCAGTGTGCGCCTCCATGCCCCAACAT
 GTATTTTAAAAGTGATGAGCTAGAGTTTGCAAAAAGTTTTATTGGAACAGTTTCAATAT
 TTTGTCTTTGTGCAACTCTGTTTACATTCTTACTTTTTTAATTGATGTTAGAAGATTCA
 GATACCCAGAGAGACCAATTATATATTACTCTGTCTGTTACAGCATTGTATCTCTTATG
 TACTTCATTGGATTTTTTGCTGGGCGATAGCACAGCCTGCAATAAGGCAGATGAGAAGC
 TAGAACTTGGTGACACTGTTGTCTTAGGCTCTCAAAATAAGGCTTGCAACCGTTTTGTTC
 ATGCTTTTTGTATTTTTTCACAATGGCTGGCACTGTGTGGTGGGTGATTCTTACCATTACT
 TGGTTCTTAGCTGCAGGAAGAAAATGGAGTTGTGAAGCCATCGAGCAAAAAGCAGTGT
 GGTTTCATGCTGTTGCATGGGGAACACCAGGTTTCTGACTGTTATGCTTCTTGCTCTGA
 ACAAAGTTGAAGGAGACAACATTAGTGGAGTTTGCTTTGTTGGCCTTTATGACCTGGAT
 GCTTCTCGCTACTTTGTACTCTTGCCACTGTGCCTTTGTGTGTTTGTGTTGGGCTCTCTCTTC
 TTTTAGCTGGCATTATTTCTTAAATCATGTTTCGACAAGTCATACAACATGATGGCCGG
 AACCAAGAAAACTAAAGAAATTTATGATTGGAATTGGAGTCTTCAGCGGCTTGTATC
 TTGTGCCATTAGTGACACTTCTCGGATGTTACGTCTATGAGCAAGTGAACAGGATTACC
 TGGGAGATAACTTGGGTCTCTGATCATTGTGCTCAGTACCATATCCCATGTCCTTATCA
 GGCAAAAGCAAAAGCTCGACCAGAATTGGCTTTATTTATGATAAAATACCTGATGACA
 TTAATTGTTGGCATCTCTGCTGTCTTCTGGGTTGGAAGCAAAAAGACATGCACAGAATG
 GGCTGGGTTTTTTAAACGAAATCGCAAGAGAGATCCAATCAGTGAAAGTCGAAGAGTA
 CTACAGGAATCATGTGAGTTTTTCTTAAAGCACAAATCTAAAGTTAAACACAAAAAGA
 AGCACTATAAACCAAGTTCACACAAGCTGAAGGTCATTTCCAAATCCATGGGAACCAG
 CACAGGAGCTACAGCAAATCATGGCACTTCTGCAGTAGCAATTACTAGCCATGATTAC
 CTAGGACAAGAACTTTGACAGAAATCCAAACCTCACCAGAAACATCAATGAGAGAG
 GTGAAAGCGGACGGAGCTAGCACCCCCAGGTAAAGAGAACAGGACTGTGGTGAACCT
 GCCTCGCCAGCAGCATCCATCTCCAGACTCTCTGGGGAACAGGTCGACGGGAAGGGCC
 AGGCAGGCAGTGTATCTGAAAGTGC GCGGAGTGAAGGAAGGATTAGTCCAAAGAGTG

ATATTACTGACACTGGCCTGGCACAGAGCAACAATTTGCAGGTCCCCAGTTCTTCAGAA
 CCAAGCAGCCTCAAAGGTTCCACATCTCTGCTTGTTCACCCAGTTTCAGGAGTGAGAAA
 AGAGCAGGGAGGTGGTTGTCATTCAGATACTTGAAGAACATTTTCTCTCGTTACTCAGA
 AGCAAATTTGTGTTACACTGGAAGTGACCTATGCACTGTTTTGTAAGAATCACTGTTAC
 GTTCTTCTTTTGCACCTAAAGTTGCATTGCCTACTGTTATACTGGAAAAAATAGAGTTC
 AAGAATAATATGACTCATTTACACAAAAGGTTAATGACAACAATATACCTGAAAACAG
 AAATGTGCAGGTTAATAATATTTTTTTAATAGTGTGGGAGGACAGAGTTAGAGGAATC
 TTCCTTTTCTATTTATGAAGATTCTACTCTTGGTAAGAGTATTTTAAGATGTACTATGCT
 ATTTTACCTTTTTGATATAAAATCAAGATATTTCTTTGCTGAAGTATTTAAATCTTATCC
 TTGTATCTTTTTATACATATTTGAAAATAAGCTTATATGTATTTGAACTTTTTTGAAATC
 CTATTCAAGTATTTTTATCATGCTATTGTGATATTTTAGCACTTTGGTAGCTTTTACACT
 GAATTTCTAAGAAAATTGTAAAATAGTCTTCTTTTATACTGTAAAAAAGATATACCAA
 AAAGTCTTATAATAGGAATTTAACTTTAAAAACCCACTTATTGATACCTTACCATCTAA
 AATGTGTGATTTTTATAGTCTCGTTTTAGGAATTCACAGATCTAAATTATGTAAGTGA
 AATAAGGTGCTTACTCAAAGAGTGTCCACTATTGATTGTATTATGCTGCTCACTGATCC
 TTCTGCATATTTAAAATAAAATGTCCTAAAGGGTTAGTAGACAAAATGTTAGTCTTTTG
 TATATTAGGCCAAGTGCAATTGACTTCCCTTTTTTAATGTTTCATGACCACCCATTGATT
 GTATTATAACCACTTACAGTTGCTTATATTTTTTGTTTTAACTTTTGTTCCTTAACATTTA
 GAATATTACATTTTGTATTATACAGTACCTTTCTCAGACATTTTGTAG

Figure 68

MEMFTFLLTCIFLPLLRGHSLFTCEPITVPRCMKMAYNMTFFPNLMGHYDQSIAAVEMEHL
 LPLANLECSNFIETFLCKAFVPTCIEQIHVPPCRKLCEKVYSDCKKLIDTFGIRWPHEELCD
 RLQYCDETVPVTFDPHTEFLGPQKKTEQVQRDIGFWCPRHLKTSGGQGYKFLGIDQCAPP
 PNMYFKSDELEFAKSFIGHTVSIFCLCATLFTFLTFLIDVRRFRYPERPIIYYSVCYSIVSLMYFI
 GFLGDESTACNKADEKLELGDTVVLGSONKACTVLFMLLYFFTMAAGTVWWVILITWFLA
 AGRKWSCEAIEQKAVWFHAVA WGTGFLTVMLLALNKVEGDNISGVCFVGLYDLASRY
 FVLLPLCLCVFVGLSLLLAGIISLNHVRQVIQHDGRNQEKLLKFMIRIGVFSGLYLVPLVTL
 GCYVYEQVNRITWEITWVSDHCRQYHIPCPYQAKAKARPELALFMIKYLMTLIVGISA
 VFVVGSKKTCTEWAGFFKRNKRDPISERRVLQESCEFFLKHNSKVKKKKHYKPSCHK
 LKVISKSMGTSTGATANHGTSVAITSHDYLGQETLTIQTSPETSMREVKADGASTPRLRE
 QDCGEPASPAASISRLSGEQVDGKGQAGSVSESARSEGRISPKSDITDTGLAQSNLQVPSS
 EPSSLKGSTSLLVHPVSGVRKEQGGGCHSDT

Figure 69

CTCTCCCAACCGCCTCGTCGCACTCCTCAGGCTGAGAGCACCGCTGCACTCGCGGCCGG
 CGATGCGGGACCCCGGCGCGGCCGCTCCGCTTTCTGTCCTGGGCCCTCTGTGCCCTGGTG
 CTGGCGCTGCTGGGCGCACTGTCCGCGGGCGCCGGGGCGCAGCCGTACCACGGAGAGA
 AGGGCATCTCCGTGCCGGACACGGCTTCTGCCAGCCCATCTCCATCCCGCTGTGCACG
 GACATCGCCTACAACCAGACCATCTGCCCAACCTGCTGGGCCACACGAACCAAGAGG
 ACGCGGGCCTCGAGGTGCACCAGTTCTACCCGCTGGTGAAGGTGCAGTGTTCTCCCGA
 ACTCCGCTTTTTCTTATGCTCCATGTATGCGCCCGTGTGCACCGTGCTCGATCAGGCCAT
 CCCGCCGTGTCGTTCTCTGTGCGAGCGCGCCCGCCAGGGCTGCGAGGCGCTCATGAAC
 AAGTTCGGCTTCCAGTGGCCCGAGCGGCTGCGCTGCGAGAACTTCCCGGTGCACGGTG
 CGGGCGAGATCTGCGTGGGCCAGAACACGTCGGACGGCTCCGGGGGGCCAGGCGGCG
 GCCCCACTGCCTACCCTACCGCGCCCTACCTGCCGGACCTGCCCTTACCGCGCTGCCC
 CCGGGGGCCTCAGATGGCAGGGGGCGTCCCGCCTTCCCCTTCTCATGCCCCCGTCACT

CAAGGTGCCCCCGTACCTGGGCTACCGCTTCCTGGGTGAGCGCGATTGTGGCGCCCCGT
GCCAACCGGGCCGTGCCAACGGCCTGATGTACTTTAAGGAGGAGGAGAGGGCGCTTCGC
CCGCCTCTGGGTGGGCGTGTGGTCCGTGCTGTGCTGCGCCTCGACGCTCTTTACCGTTC
TCACCTACCTGGTGGACATGCGGCGCTTCAGCTACCCAGAGCGGCCCATCATCTTCCTG
TCGGGCTGCTACTTCATGGTGGCCGTGGCGCACGTGGCCGGCTTCCTTCTAGAGGACCG
CGCCGTGTGCGTGGAGCGCTTCTCGGACGATGGCTACCGCACGGTGGCGCAGGGCACC
AAGAAGGAGGGCTGCACCATCCTCTTCATGGTGTCTACTTCTTCGGCATGGCCAGCTC
CATCTGGTGGGTCACTTCTGTCTCTCACTTGGTTCCTGGCGGCCGGCATGAAGTGGGGCC
ACGAGGCCATCGAGGCCAACTCGCAGTACTTCCACCTGGCCGCGTGGGCCGTGCCCGC
CGTCAAGACCATCACTATCCTGGCCATGGGCCAGGTAGACGGGGACCTGCTGAGCGGG
GTGTGCTACGTTGGCCTCTCCAGTGTGGACGCGCTGCGGGGCTTCGTGCTGGCGCCTCT
GTTGCTTACCTCTTCATAGGCACGTCTTCTTGCTGGCCGGCTTCGTGTCCCTCTTCCG
TATCCGCACCATCATGAAACACGACGGCACCAAGACCGAGAAGCTGGAGAAGCTCAT
GGTGCGCATCGGCGTCTTCAGCGTGTCTACACAGTGCCCGCCACCATCGTCTGGCCT
GCTACTTCTACGAGCAGGCCTTCCGCGAGCACTGGGAGCGCACCTGGCTCCTGCAGAC
GTGCAAGAGCTATGCCGTGCCCTGCCCCGCCCGGCCACTTCCCGCCCATGAGCCCCGACT
TCACCGTCTTCATGATCAAGTACCTGATGACCATGATCGTCGGCATCACCACTGGCTTC
TGGATCTGGTCGGGCAAGACCCTGCAGTCGTGGCGCCGCTTCTACCACAGACTTAGCC
ACAGCAGCAAGGGGGAGACTGCGGTATGAGCCCCGGCCCCCTCCCCACCTTTCCACCC
CAGCCCTCTTGCAAGAGGAGAGGCACGGTAGGGAAAAGAACTGCTGGGTGGGGGCCCT
GTTTCTGTAACTTTCTCCCCCTCTACTGAGAAGTGACCTGGAAGTGAGAAGTTCTTTGC
AGATTTGGGGCGAGGGGTGATTTGGAAGAAAGACCTGGGTGGAAGCGGTTTGGAT
GAAAAGATTTCAAGCAAAGACTTGCAGGAAGATGATGATAACGGCGATGTGAATCGTC
AAAGGTACGGGCCAGCTTGTGCCTAATAGAAGGTTGAGACCAGCAGAGACTGCTGTGA
GTTTCTCCCGGCTCCGAGGCTGAACGGGGACTGTGAGCGATCCCCCTGCTGCAGGGCG
AGTGGCCTGTCCAGACCCCTGTGAGGCCCGGGAAAGGTACAGCCCTGTCTGCGGTGG
CTGCTTTGTTGGAAAGAGGGAGGGCCTCCTGCGGTGTGCTTGTCAAGCAGTGGTCAAA
CCATAATCTCTTTTCACTGGGGCCAACTGGAGCCCAGATGGGTAAATTTCCAGGGTCA
GACATTACGGTCTCTCCTCCCCCTGCCCCCTCCCGCCTGTTTTTCTCCTCCCGTACTGCTTC
AGGTCTTGTAATAAAGCATTGGAAGTCTTGGGAGGCCTGCCTGCTAGAATCCTAATG
TGAGGATGCAAAAGAAATGATGATAACATTTTGAGATAAGGCCAAGGAGACGTGGAG
TAGGTATTTTTGCTACTTTTTCATTTTTCTGGGGAAGGCAGGAGGCAGAAAGACGGGTGT
TTTATTTGGTCTAATACCCTGAAAAGAAGTGATGACTTGTGCTTTTCAAAACAGGAAT
GCATTTTTCCCTTGTCTTTGTTGTAAGAGACAAAAGAGGAAACAAAAGTGTCTCCCTG
TGAAAGGCATAACTGTGACGAAAGCAACTTTTATAGGCAAAGCAGCGCAAATCTGAG
GTTTCCCGTTGGTTGTTAATTTGGTTGAGATAAACATTCCTTTTTAAGGAAAAGTGAAG
AGCAGTGTGCTGTACACACCGTTAAGCCAGAGGTTCTGACTTCGCTAAAGGAAATGT
AAGAGGTTTTGTTGTCTGTTTTAAATAAATTTAATTCGGAACACATGATCCAACAGACT
ATGTTAAATATTCAGGGAAATCTCTCCCTTCATTTACTTTTTCTTGCTATAAGCCTATA
TTTAGGTTTTCTTTCTATTTTTTCTCCCATTTGGATCCTTTGAGGTAACAAAACATAAT
GTCCTCAGCCTCATAATAAAGGAAAGTTAATTAACATCATCCATATGCTGACCCTGT
CTCTGTGTGGTTGGGTTGGGAGGCGATCAGCAGATACCATAGTGAACGAAGAGGAAGG
TTTGAACCATGGGCCCCATCTTTAAAGAAAGTCATTAAAGAAAGGTAACTTCAAAGT
GATTCTGGAGTTCTTTGAAATGTGCTGGAAGACTTAAATTTATTAATCTTAAATCATGT
ACTTTTTTTCTGTAATAGAACTCGGATTCTTTTGCATGATGGGGTAAAGCTTAGCAGAG
AATCATGGGAGCTAACCTTTATCCCACCTTTGACACTACCCTCCAATCTTGCAACACTA
TCCTGTTTCTCAGAACAGTTTTTAAATGCCAATCATAGAGGGTACTGTAAAGTGTACAA
GTTACTTTATATATGTAATGTTCACTTGAGTGGAAGTGTCTTTTACATTAAAGTTAAAT
CGATCTTGTGTTTCTTCAACCTTCAAACTATCTCATCTGTGAGATTTTTAAACTCCAA
CACAGGTTTTGGCATCTTTGTGCTGTATCTTTAAGTGCATGTGAAATTTGTAAATAG
AGATAAGTACAGTATGTATATTTGTAAATCTCCCATTTTTGTAAAGAAATATATATTG

TATTTATACATTTTACTTTGGATTTTGTGTTTGGCTTTAAAGGTCTACCCCACTTTA
TCACATGTACAGATCACAAATAAATTTTTTAAATAC

Figure 70

MRDPGAAAPLSSLGLCALVLALLGALSAGAGAQPYPHGEKGISVPDHGFCQPISIPLCTDIAY
NQILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCTVLDQAIPPCRS
ERARQGCEALMNKFGFQWPERLRNENFPVHGAGEICVGQNTSDGSGGPGGGPTAYPTAPY
LPDLPFTALPPGASDGRGRPAFPFSCPRQLKVPPYLYRFLGERDCGAPCEPGRANGLMYF
KEEERRFARLWVGWVSVLCCASTLFTVLTLYLVDMMRRFSYPERPIIFLSGICYFMVAVAHVA
GFLLDRAVCVERFSDDGYRTVAQGTKKEGCTILFMVLYFFGMASIIWWVILSLTWFLAA
GMKWGHEAIEANSQYFHLAAWAVPAVKTITILAMGQVDGDLISGVCYVGLSSVDA
LRGFVLAPLFFVYLFITGSFLLAGFVSLFRIRTIMKHDGTEKLEKLMVRIGVFSVLYTVPAT
IVLACYFYEQAFREHWERTWLLQTCKSYAVPCPPGHFPPMSPDFTVFMIKYLMTMIVGIT
GFWIWSGKTLQSWRRFYHRLSHSSKGETAV

Figure71

ACAGCATGGAGTGGGGTTACCTGTTGGAAGTGACCTCGCTGCTGGCCGCCTTGGCGCT
GCTGCAGCGCTCTAGCGGCGCTGCGGCCGCTCGGCCAAGGAGCTGGCATGCCAAGAG
ATCACCGTGCCGCTGTGTAAGGGCATCGGCTACAACCTACACCTACATGCCCAATCAGTT
CAACCACGACACGCAAGACGAGGCGGGCCTGGAGGTGCACCAAGTCTTGGCCGCTGGT
GAGATCCAGTGCTCGCCCGATCTCAAGTTCTTCTGTGCAGCATGTACACGCCCATCTG
CCTAGAGGACTACAAGAAGCCGCTGCGGCCCTGCGCTCGGTGTGCGAGCGCGCCAAG
GCCGGCTGCGCGCCGCTCATGCGCCAGTACGGCTTCGCTGGCCCGACCGCATGCGCT
GCGACCGGCTGCCCGAGCAAGGCAACCCTGACACGCTGTGCATGGACTACAACCGCAC
CGACCTAACCACCGCCGCGCCAGCCCGCCGCGCCGCTGCGCCCGCCGCGCCCGGC
GAGCAGCCGCCTTCGGGCAGCGGCCACGGCCGCGCCGCGGGGGCCAGGCCCGCGCAC
GCGGAGGCGGCAGGGGCGGTGGCGGCGGGGACGCGGCGGCGCCCCAGCTCGCGGCG
GCGGCGGTGGCGGGAAGGCGCGGCCCTGGCGGCGGCGCGGCTCCCTGCGAGCCCG
GGTGCCAGTGCCGCGCGCCTATGGTGAGCGTGTCCAGCGAGCGCCACCCGCTCTACAA
CCGCGTCAAGACAGGCCAGATCGCTAACTGCGCGCTGCCCTGCCACAACCCCTTTTTCA
GCCAGGACGAGCGCGCCTTACCGTCTTCTGGATCGGCCTGTGGTCGGTGCTCTGCTTC
GTGTCCACCTTCGCCACCGTCTCCACCTTCTTATCGACATGGAGCGCTTCAAGTACCC
GGAGCGGCCATTATCTTCTCTCGGCCTGCTACCTCTTCGTGTGGTGCGGCTACCTAG
TGCGCTGTGGTGGCGGGCCACGAGAAGGTGGCGTGCAGCGGTGGCGCGCCGGGCGCGG
GGGGCGCTGGGGGCGCGGGCGGCGGCGGGCGGCGGGCGCGGGCGCGGGCGCGGGCG
CGGGCGGCCCGGGCGGGCGGCGGCGAGTACGAGGAGCTGGGCGCGGTGGAGCAGCACG
TGCGCTACGAGACCACCGGCCCGCGCTGTGCACCGTGGTCTTCTTGTGGTCTACTTC
TTCGGCATGGCCAGCTCCATCTGGTGGGTGATCTTGTGCTCACATGGTTCCTGGCGGC
CGGTATGAAGTGGGGCAACGAAGCCATCGCCGGCTACTCGCAGTACTTCCACCTGGCC
GCGTGGCTTGTGCCCAGCGTCAAGTCCATCGCGGTGCTGGCGCTCAGCTCGGTGGACG
GCGACCCGGTGGCGGGCATCTGCTACGTGGGCAACCAGAGCCTGGACAACCTGCGCGG
CTTCGTGCTGGCGCCGCTGGTCATCTACCTCTTCATCGGCACCATGTTCTCTGCTGGCCG
GCTTCGTGTCCCTGTTCCGCATCCGCTCGGTGATCAAGCAACAGGACGGCCCCACCAAG
ACGCACAAGCTGGAGAAGCTGATGATCCGCTGGGCCTGTTACCGTGCTCTACACCG
TGCCCGCCGCGGTGGTGGTGGCTGCTCTTCTACGAGCAGCACAACCGCCCGCGCTG
GGAGGCCACGCACAACCTGCCCCTGCGGGACCTGCAGCCCGACCAAGGACGCAG
GCCCGACTACGCCGTCTTCATGCTCAAGTACTTCATGTGCTAGTGGTGGGCATCACCT
CGGGCGTGTGGGTCTGGTCCGGCAAGACGCTGGAGTCTGGCGCTCCCTGTGCACCCG
CTGCTGCTGGGCCAGCAAGGGCGCCGCGGTGGGCGGGGGCGCGGGCGCCACGGCCG
GGGGGGTGGCGGCGGGCCGGGGGGCGGCGGCGGCGGGGGACCCGGCGGCGGGGG

GGCCGGGCGGCGGCGGGGGCTCCCTCTACAGCGACGTCAGCACTGGCCTGACGTGGCG
GTCGGGCACGGCGAGCTCCGTGTCTTATCCAAAGCAGATGCCATTGTCCCAGGTCTGA
GCGGAGGGGAGGGGGCGCCAGGAGGGGTGGGGAGGGGGGCGAGGAGACCCAAGTG
CAGCGAAGGGACACTTGATGGGCTGAGGTTCCACCCCTTCACAGTGTTGATTGCTATT
AGCATGATAATGAACTCTTAATGGTATCCATTAGCTGGGACTTAAATGACTCACTTAGA
ACAAAGTACCTGGCATTGAAGCCTCCCAGACCCAGCCCCCTTTTCTCCATTGATGTGCG
GGGAGCTCCTCCCGCCACGCGTTAATTTCTGTTGGCTGAGGAGGGTGGACTCTGCGGCG
TTTCCAGAACCCGAGATTTGGAGCCCTCCCTGGCTGCACTTGGCTGGGTTTGCAGTCAG
ATACACAGATTTACCTGGGAGAACCTCTTTTCTCCCTCGACTCTTCCTACGTAAACTC
CCACCCCTGACTTACCCTGGAGGAGGGGTGACCGCCACCTGATGGGATTGCACGGTTT
GGGTATTCTTAATGACCAGGCAAATGCCTTAAGTAAACAAACAAGAAATGTCTTAATT
ATACACCCACGTAAATACGGGTTTCTTACATTAGAGGATGTATTTATATAATTATTG
TTAAATTGTAAAAAAGTGTAAAATATGTATATATCCAAAGATATAGTGTGTAC
ATTTTTTTGTAAAAAGTTTAGAGGCTTACCCCTGTAAGAACAGATATAAGTATTCTATT
TTGTCAATAAAATGACTTTTGATAAATGATTTAACCATTGCCCTCTCCCCCGCCTCTTCT
GAGCTGTCACCTTTAAAGTGCTTGCTAAGGACGCATGGGGAAAATGGACATTTTCTGG
CTTGTCATTCTGTACACTGACCTTAGGCATGGAGAAAATTACTTGTTAAACTCTAGTTC
TTAAGTTGTTAGCCAAGTAAATATCATTGTTGAACTGAAATCAAATGAGTTTTTGCA
CCTTCCCCAAAGACGGTGTTTTTCATGGGAGCTCTTTTCTGATCCATGGATAACAACCTC
TCACTTTAGTGATGTAAATGGAACCTCTGCAAGGCAGTAATCCCCTTAGGCCTTGTT
ATTTATCCTGCATGGTATCACTAAAGGTTTCAAACCCCTGAAAAAAA

Figure 72

MEWGYLLEVTSLLAALALLQRSSGAAAASAKELACQEITVPLCKGIGYNYTYMPNQFNHD
TQDEAGLEVHQFWPLVEIQCSFDLKFFLCMYTPICLEDYKKPLPPCRSVCERAKAGCAPL
MRQYGFAPWDRMRCDRLEQGNPDTLCMDYNRTDLTTAAPSPPRRLPPPPGEQPPSGSG
HGRPPGARPPHRGGGRGGGGDAAAPPARGGGGGGKARPPGGGAAPCEPGCQCRAPMVS
VSSERHPLYNRVKTGQIANCALPCHNPFFSQDERAFTVFWIGLWSVLCFVSTFATVSTFLID
MERFKYPERPIIFLSACYLFVSVGYLVRLVAGHEKVACSGGAPGAGGAGGAGGAAAGAG
AAGAGAGGPGGRGEYEELGAVEQHVRVYETTGPALCTVVFLVYFFGMASSIWWVILSLT
WFLAAGMKWGNELAGYSQYFHLLAAWLVPVSKSIAVLALSSVDGDPVAGICYVGNQSLD
NLRGFVLAPLVIYLFITMFLLAGFVSLFRIRSVIKQQDGP TKTHKLEKLMIRLGLFTVLYTV
PAAVVVACLFIYEQHNRPRWEATHNCPCLRDLPDQARRPDYAVFMLKYFMCCLVVGITSG
VWVWSGKTLESWRSCLTRCCWASKGA AVGGGAGATAAGGGGGPGGGGGGGPGGGGGP
GGGGGSLYSDVSTGLTWRSGTASSVSYPKQMPLSQV

Figure 73

CCGCCTTCGGCCCCGGGCCTCCCGGGATGGCCGTGGCGCCTCTGCGGGGGGCGCTGCTG
CTGTGGCAGCTGCTGGCGGCGGGCGGGCGCGGCACTGGAGATCGGCCGCTTCGACCCGG
AGCGCGGGCGCGGGGCTGCGCCGTGCCAGGCGGTGGAGATCCCCATGTGCCGCGGCAT
CGGCTACAACCTGACCCGCATGCCAACCTGCTGGGCCACACGTGCGAGGGCGAGGCG
GCTGCCGAGCTAGCGGAGTTGCGCGCCGCTGGTGCAGTACGGCTGCCACAGCCACCTGC
GCTTCTTCTGTGCTCGCTCTACGCGCCCATGTGCACCGACCAGGTCTCGACGCCCAT
CCCGCCTGCCGGCCCATGTGCGAGCAGGCGCGCCTGCGCTGCGCGCCCATCATGGAGC
AGTTCAACTTCGGCTGGCCGGA CTGCTCGACTGCGCCCGGCTGCCACGCGCAACGA
CCCGCACGCGCTGTGCATGGAGGCGCCCGAGAACGCCACGGCCGGCCCCGCGGAGCCC
CACAAGGGCCTGGGCATGCTGCCCGTGGCGCCGCGGCCCGCGCGCCCTCCCGGAGACC

TGGGCCCCGGGCGCGGGCGGCAGTGGCACCTGCGAGAACCCCGAGAAGTTCCAGTACGT
 GGAGAAGAGCCGCTCGTGCGCACCGCGCTGCGGGCCCGGCGTCGAGGTGTTCTGGTCC
 CGGCGCGACAAGGACTTCGCGCTGGTCTGGATGGCCGTGTGGTCGGCGCTGTGCTTCTT
 CTCCACCGCCTTCACTGTGCTCACCTTCTTGCTGGAGCCCCACCGCTTCCAGTACCCCG
 AGCGCCCCATCATCTTCTCTCCATGTGCTACAACGTCTACTCGCTGGCCTTCTGATCC
 GTGCGGTGGCCGGAGCGCAGAGCGTGGCCTGTGACCAGGAGGCGGGCGCGCTCTACGT
 GATCCAGGAGGGCCTGGAGAACACGGGCTGCACGCTGGTCTTCTACTGCTCTACTAC
 TTCGGCATGGCCAGCTCGCTCTGGTGGGTGGTCCTGACGCTCACCTGGTTCCTGGCTGC
 CGGGAAGAAATGGGGCCACGAGGCCATCGAGGCCACGGCAGCTATTTCCACATGGCT
 GCCTGGGGCCTGCCCCGCGCTCAAGACCATCGTCATCCTGACCCTGCGCAAGGTGGCGG
 GTGATGAGCTGACTGGGCTTTGCTACGTGGCCAGCACGGATGCAGCAGCGCTCACGGG
 CTTCTGTGCTGGTGGCCCTCTCTGGCTACCTGGTGTGGGCAGTAGTTTCTCTGACCG
 GCTTCGTGGCCCTCTTCCACATCCGCAAGATCATGAAGACGGGCGGCACCAACACAGA
 GAAGCTGGAGAAGCTCATGGTCAAGATCGGGGTCTTCTCCATCCTCTACACGGTGGCC
 GCCACCTGCGTCATCGTTTGCTATGTCTACGAACGCCTCAACATGGACTTCTGGCGCCT
 TCGGGCCACAGAGCAGCCATGCGCAGCGGCCGCGGGGCCCGGAGGCCGGAGGGACTG
 CTCGCTGCCAGGGGGCTCGGTGCCACCGTGGCGGTCTTCATGCTCAAAATTTTCATGT
 CACTGGTGGTGGGGATCACCAGCGGCGTCTGGGTGTGGAGCTCCAAGACTTTCCAGAC
 CTGGCAGAGCCTGTGCTACCGCAAGATAGCAGCTGGCCGGGGCCCGGGCCAAGGCCTGC
 CGCGCCCCCGGGAGCTACGGACGTGGCACGCACTGCCACTATAAGGCTCCCACCGTGG
 TCTTGACATGACTAAGACGGACCCCTCTTTGGAGAACCCACACACCTCTAGCCACAC
 AGGCCTGGCGCGGGGTGGCTGCTGCCCCCTCCTTGCCCTCCACGCCCTGCCCCCTGCAT
 CCCCTAGAGACAGCTGACTAGCAGCTGCCCAGCTGTCAAGGTCAGGCAAGTGAGCACC
 GGGGACTGAGGATCAGGGCGGGACCCCGTGAGGCTCATTAGGGGAGATGGGGGTCTC
 CCCTAATGCGGGGGCTGGACCAGGCTGAGTCCCCACAGGGTCCTAGTGAGGATGTGG
 AGGGGCGGGGCAGAGGGGTCCAGCCGGAGTTTATTTAATGATGTAATTTATTGTTGCG
 TTCCTCTGGAAGCTGTGACTGGAATAAACCCCGCGTGGCACTGCTGATCCTCTCTGGC
 TGGGAAGGGGGAAGGTAGGAGGTGAGGC

Figure 74

MAVAPLRGALLLWQLLAAGGALEIGRFDPERGRGAAPCQAVEIPMCRGIGYNLTRMPNL
 LGHTSQGEAAAEALAEFAPLVQYGCHSHLRFFLCSLYAPMCTDQVSTPIPACRPMCEQARLR
 CAPIMEQFNFGWPDSLDCARLPTRNDPHALCMEAPENATAGPAEPHKGLGMLPVAPRPAR
 PPGDLGPGAGSGTCENPEKFQYVEKSRSCAPRCGPGVEVFWSSRRDKDFALVWMAVWSA
 LCFFSTAFTVLTFLLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAGAQSVACDQAEAGALY
 VIQEGLENTGCTLVFLLLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMA
 AWGLPALKTIVILTLRKVAGDELTGLCYVASTDAAALTGFVLVPLSGYLVLGSSFLTG
 FVALFHIRKIMKTGGTNTTEKLEKLMVKIGVFSILYTVPATCVIVCYVYERLNMDFWRLRAT
 EQPCAAAAGPGGRRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSSKTFQTWQSLC
 YRKIAAGRARAKACRAPGSYGRGTHCHYKAPTIVLHMTKTDPSLENPTH

Figure 75

ACACGTCCAACGCCAGCATGCAGCGCCCGGGCCCCCGCCTGTGGCTGGTCCTGCAGGT
 GATGGGCTCGTGCGCCGCCATCAGCTCCATGGACATGGAGCGCCCGGGCGACGGCAAA
 TGCCAGCCCATCGAGATCCCGATGTGCAAGGACATCGGCTACAACATGACTCGTATGC
 CCAACCTGATGGGCCACGAGAACCAGCGCGAGGCAGCCATCCAGTTGCACGAGTTCG
 GCCGCTGGTGGAGTACGGCTGCCACGGCCACCTCCGCTTCTTCTGTGCTCGCTGTACG
 CGCCGATGTGCACCGAGCAGGTCTCTACCCCCATCCCCGCCTGCCGGGTGATGTGCGA
 GCAGGCCCGGCTCAAGTGCTCCCCGATTATGGAGCAGTTCAACTTCAAGTGGCCCGAC

TCCCTGGACTGCCGGAAACTCCCCAACAAGAACGACCCCAACTACCTGTGCATGGAGG
CGCCCAACAACGGCTCGGACGAGCCCACCCGGGGCTCGGGCCTGTTCCCGCCGCTGTT
CCGGCCGCAGCGGCCCCACAGCGCGCAGGAGCACCCGCTGAAGGACGGGGGGCCCGG
GCGCGGGCGGCTGCGACAACCCGGGCAAGTTCCACCACGTGGAGAAGAGCGCGTCGTG
CGCGCCGCTCTGCACGCCCCGGCGTGGACGTGTACTGGAGCCGCGAGGACAAGCGCTTC
GCAGTGGTCTGGCTGGCCATCTGGGCGGTGCTGTGCTTCTTCTCCAGCGCCTTCACCGT
GCTCACCTTCCTCATCGACCCGGCCCCGCTTCCGCTACCCCGAGCGCCCCATCATCTTCC
TCTCCATGTGCTACTGCGTCTACTCCGTGGGCTACCTCATCCGCCTCTTCGCCGGCGCC
GAGAGCATCGCCTGCGACCGGGACAGCGGCCAGCTCTATGTCATCCAGGAGGGACTGG
AGAGCACCGGCTGCGACGCTGGTCTTCTGTCCTCTACTACTTCGGCATGGCCAGCTCG
CTGTGGTGGGTGGTCCTCACGCTCACCTGGTTCCTGGCCGCGCGCAAGAAGTGGGGCC
ACGAGGCCATCGAAGCCAACAGCAGCTACTTCCACCTGGCAGCCTGGGCCATCCCGGC
GGTGAAGACCATCCTGATCCTGGTCATGCGCAGGGTGGCGGGGGACGAGCTCACCGGG
GTCTGCTACGTGGGCAGCATGGACGTCAACGCGCTCACCGGCTTCGTGCTCATTCCCCT
GGCCTGCTACCTGGTCATCGGCACGTCTTCATCCTCTCGGGCTTCGTGGCCCTGTTCC
ACATCCGGAGGGTGTGAAGACGGGCGGCGAGAACACGGACAAGCTGGAGAAGCTCA
TGGTGCGTATCGGGCTCTTCTCTGTGCTGTACACCGTGCCGGCCACCTGTGTGATCGCC
TGCTACTTTTACGAACGCCTCAACATGGATTACTGGAAGATCCTGGCGGCGCAGCACA
AGTGCAAAATGAACAACCAGACTAAAACGCTGGACTGCCTGATGGCCGCCTCCATCCC
CGCCGTGGAGATCTTCATGGTGAAGATCTTTATGCTGCTGGTGGTGGGGATCACCAGCG
GGATGTGGATTTGGACCTCCAAGACTCTGCAGTCCTGGCAGCAGGTGTGCAGCCGTAG
GTAAAGAAGAAGAGCCGGAGAAAACCGGCCAGCGTGATCACCAGCGGTGGGATTTA
CAAAAAAGCCAGCATCCCCAGAAAACCTACCACGGGAAATATGAGATCCCTGCCCAG
TCGCCACCTGCGTGTGAACAGGGCTGGAGGGGAAGGGCACAGGGGCGCCCGGAGCTA
AGATGTGGTGCTTTTCTTGTTGTGTTTTTCTTCTTCTTCTTTTTTTTTTTTATAA
AAGCAAAAGAGAAATACATAAAAAAGTGTTTACCCTGAAATTCAGGATGCTGTGATAC
ACTGAAAGGAAAAATGTACTTAAAGGGTTTTGTTTTGTTTTGGTTTTCCAGCGAAGGGA
AGCTCCTCCAGTGAAGTAGCCTCTTGTGTAATAATTTGTGGTAAAGTAGTTGATTCAG
CCCTCAGAAGAAAACCTTTTGTTTAGAGCCCTCCGTAAATATACATCTGTGTATTTGAGT
TGGCTTTGCTACCCATTTACAAATAAGAGGACAGATAACTGCTTTGCAAATTCAGAGC
CTCCCCTGGGTAAACAAATGAGCCATCCCCAGGGGCCACCCCCAGGAAGGCCACAGTG
CTGGGCGGCATCCCTGCAGAGGAAAGACAGGACCCGGGGCCCGCCTCACACCCCAAGTG
GATTTGGAGTTGCTTAAATAGACTCTGGCCTTCACCAATAGTCTCTCTGCAAGACAGA
AACCTCCATCAAACCTCACATTTGTGAACCTCAAACGATGTGCAATACATTTTTTTCTCTT
TCCTTGAAAATAAAAAAGAGAAACAAGTATTTTGCTATATATAAAGACAACAAAAGAAA
TCTCCTAACAAAAGAACTAAGAGGCCAGCCCTCAGAAACCCTTCAGTGCTACATTTT
GTGGCTTTTTAATGGAAACCAAGCCAATGTTATAGACGTTTGGACTGATTTGTGGAAAG
GAGGGGGGAAGAGGGGAGAAGGATCATTCAAAAGTTACCCAAAGGGCTTATTGACTCTT
TCTATTGTAAACAAATGATTTCCACAAACAGATCAGGAAGCACTAGGTTGGCAGAGA
CACTTTGTCTAGTGTATTCTCTTCACAGTGCCAGGAAAGAGTGGTTTCTGCGTGTGTAT
ATTTGTAATATATGATATTTTTCATGCTCCACTATTTTATTAAAAATAAAATATGTTCTT
TAAAAAAA

Figure 76

MQRPGPRLWLVLQVMGSCAAISSMDMERPGDGKCPQIEIPMCKDIGYNMTRMPNLMGHE
NQREAAIQLHEFAPLVEYGCHGHLRFFLCSLYAPMCTEQVSTPIACRVMCEQARLKCSPI
MEQFNFKWPDSLDCRKLPNKNDPNYLCMEAPNNGSDEPTRGSGLFPPFRPQRPHSAQEH
PLKDGPGPRGGCDNPGKFHHVEKSASCAPLCTPGVDVYWSREDKRFVWLAIWAVLCF
FSSAFTVLTLIDPARFRYPERPIIFLSMCYCVYSVGYLIRLFAGAESACDRDSGQLYVIQEG
LESTGCTLVFLVLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEANSSYFHLAAWAIP
AVKTILILVMRRVAGDELTVGCYVGSMDVNALTGFVLIPLACYLVIGTSFILSGFVAL

FHIRRVMKTGGENTDKLEKLMVRIGLFSVLYTVPATCVIACYFYERLNM DYWKILAAQHK
CKMNNQTKTLDCLMAASIPAVEIFMVKIFMLLVVGITSGMWIWT SKTLQSWQQVCSRRLK
KKSRRKPASVITSGGIYKKAQHPQKTHHGKYEIPAQSPTCV

Figure 77

CCTGCAGCCTCCGGAGTCAGTGCCGCGCGCCCGCCGCCCCGCGCCTTCCTGCTCGCCGC
ACCTCCGGGAGCCGGGGCGCACCCAGCCCGCAGCGCCGCTCCCCGCCCCGCGCCGCT
CCGACCGCAGGCCGAGGGCCGCACTGGCCGGGGGGACCGGGCAGCAGCTTGCGGCC
GCGGAGCCGGGCAACGCTGGGGACTGCGCCTTTTGTCCCCGGAGGTCCCTGGAAGTTT
GCGGCAGGACGCGCGCGGGGAGGCGGCGGAGGCAGCCCCGACGTGCGGGAGAACAGG
GCGCAGAGCCGGCATGGGCATCGGGCGCAGCGAGGGGGGCCCGCGGGGGCCCTGGG
CGTGCTGCTGGCGCTGGGCGCGGCGCTTCTGGCCGTGGGCTCGGCCAGCGAGTACGAC
TACGTGAGCTTCCAGTCGGACATCGGCCCCGTACCAGAGCGGGCGCTTCTACACCAAGC
CACCTCAGTGCGTGACATCCCCGCGGACCTGCGGCTGTGCCACAACGTGGGCTACAA
GAAGATGGTGCTGCCAACCTGCTGGAGCACGAGACCATGGCGGAGGTGAAGCAGCA
GGCCAGCAGCTGGGTGCCCTGCTCAACAAGAACTGCCACGCCGGGACCCAGGTCTTC
CTCTGCTCGCTCTTCGCGCCCGTCTGCCTGGACCGGCCATCTACCCGTGTCGCTGGCT
CTGCGAGGCCGTGCGCGACTCGTGCGAGCCGGTCATGCAGTTCTTCGGCTTCTACTGGC
CCGAGATGCTTAAGTGTGACAAGTTCCCGGAGGGGGACGTCTGCATCGCCATGACGCC
GCCCAATGCCACCGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCCTCCCTGTGAC
AACGAGTTGAAATCTGAGGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGCACTGA
GGATGAAAATAAAAGAAGTGAAAAAAGAAAATGGCGACAAGAAGATTGTCCCAAGA
AGAAGAAGCCCCTGAAGTTGGGGCCCATCAAGAAGAAGGACCTGAAGAAGCTTGTGC
TGTACCTGAAGAATGGGGCTGACTGTCCCTGCCACCAGCTGGACAACCTCAGCCACCA
CTTCCTCATCATGGGCCGCAAGGTGAAGAGCCAGTACTTGCTGACGGCCATCCACAAG
TGGGACAAGAAAAACAAGGAGTTCAAAAACCTTCATGAAGAAAATGAAAAACCATGAG
TGCCCCACCTTTTCAGTCCGTGTTTAAGTGATTCTCCCGGGGGCAGGGTGGGGAGGGAG
CCTCGGGTGGGGTGGGAGCGGGGGGGACAGTGCCCGGGAACCCGTGGTCACACACAC
GCACTGCCCTGTCAGTAGTGACATTGTAATCCAGTCGGCTTGTTCCTTGACGATTCCC
GCTCCCTTTCCCTCCATAGCCACGCTCCAACCCCCAGGGTAGCCATGGCCGGGTAAAG
CAAGGGCCATTTAGATTAGGAAGGTTTTTAAGATCCGCAATGTGGAGCAGCAGCCACT
GCACAGGAGGAGGTGACAAACCATTTC AACAGCAACACAGCCACTAAAACACAAAA
AGGGGGATTGGGCGGAAAGTGAGAGCCAGCAGCAAAAACTACATTTTGCAACTTGTG
GTGTGGATCTATTGGCTGATCTATGCCTTTC AACTAGAAAATTCTAATGATTGGCAAGT
CACGTTGTTTTAGGTCCAGAGTAGTTTCTTTCTGTCTGCTTTAAATGGAAACAGACTC
ATACCACACTTACAATTAAGGTCAAGCCCAGAAAGTGATAAGTGACAGGGAGGAAAAG
TGCAAGTCCATTATCTAATAGTGACAGCAAAGGGACCAGGGGAGAGGCATTGCCTTCT
CTGCCACAGTCTTTCCGTGTGATTGTCTTTGAATCTGAATCAGCCAGTCTCAGATGCC
CCAAAGTTTCGGTTCCTATGAGCCCGGGGCATGATCTGATCCCCAAGACATGTGGAGG
GGCAGCCTGTGCCTGCCTTTGTGTCAGAAAAAGGAAACCACAGTGAGCCTGAGAGAGA
CGGCGATTTTCGGGCTGAGAAGGCAGTAGTTTTTCAAAACACATAGTTA

Figure 78

MGIGRSEGGRGAALGVLLALGAALLAVGSASEYDYVSFQSDIGPYQSGRFYTKPPQCVDI
PADLRLCHNVGYKKMVLPLNLEHETMAEVKQQASSWVPLLNKNCHAGTQVFLCSLFAPV
CLDRPIYPCRWLCEAVRDSCEPVMQFFGFYWPEMLKCDKFPEGDVCIAMTPPNATEASKP
QGTTVCPPCDNELKSEAIIHLCASEFGLSLKMIVGSSSHNSCCTLGPSHPNSSKRQEQELGTP
ERRLG YGLLLHFIQGNLPPPCAQARSRMRLKTEATPLALGRSAPGLFADCPERPLPVCSFPH

HTEEVGKLRHSFLLQVKGFMSKGLCAPSTLRYLYLKTSMQHVHQEYQAHSAQVWANM
PPAERCKDEEDKAMFSK

Figure 79

GAATTCGTTTCAGCCTGGTTAAGTCCAAGCTGGCTCATTCTGCTCCCCCGGGTCGGAGCC
CCCCGGAGCTGCGCGCGGGCTTGCAGCGCCTCGCCCCGCGCTGTCTCCCGGTGTCCCGC
TTCTCCGCGCCCCAGCCGCGGGCTGCCAGCTTTTCGGGGCCCCGAGTCGCACCCAGCGA
AGAGAGCGGGCCCCGGGACAAGCTCGAACTCCGGCCGCTCGCCCTTAACCAGCTCCGT
CCCTCTACCCCTAGGGGTGCGCGCCACGATGCTGCAGGGCCCTGGCTCGCTGCTGCTG
CTCTTCCTCGCCTCGCACTGCTGCCTGGGCTCGGCGCGCGGGCTCTTCCTCTTTGGCCA
GCCCCACTTCTCCTACAAGCGCAGCAATTGCAAGCCCATCCCGGCCAACCTGCAGCTG
TGCCACGGCATCGAATACCAGAACATGCGGCTGCCAACCTGCTGGGCCACGAGACCA
TGAAGGAGGTGCTGGAGCAGGCCGCGCTTGGATCCCGCTGGTCATGAAGCAGTGCCA
CCCGGACACCAAGAAGTTCCTGTGCTCGCTCTTCGCCCCCGTCTGCCTCGATGACCTAG
ACGAGACCATCCAGCCATGCCACTCTCGNTGCGTGCAAGGTGAAGGATCGCTGCGCCCC
GGTCATGTCCGCTTCCCCTGGCCGACATGCTTGAGTGCGACCGTTTCCCCCAGGACA
ACGACCTTTGCATCCCCCTCGCTAGCAGCGACCACCTCCTGCCAGCCACCGAGGAAGC
TCCAAAGGTATGTGAAGCCTGCAAAAATAAAAATGATGATGACAACGACATAATGGA
AACGCTTTGTAAAAATGATTTTGCCTGAAAATAAAAGTGAAGGAGATAACCTACATC
AACCGT

Figure 80

MLQGPGLLLLLFLASHCCLGSARGLFLFGQPDFSYKRSNCKPIPANLQLCHGIEYQNMRLP
NLLGHETMKEVLEQAGAWIPLVMKQCHPDTKKFLCSLFAPVCLDDLDETIQPCHSRCVQV
KDRCAPVMSAFPWPDMLECDRFPQDNDLCIPLASSDHLLPATEEAPKVCEACKNKNDNDDN
DIMETLCKNDFALKIKVKEITYINR

Figure 81

CCGGGTTCGGAGCCCCCGGAGCTGCGCGCGGGCTTGCAGCGCCTCGCCCCGCGCTGTCC
TCCCGGTGTCCCGCTTCTCCGCGCCCCAGCCGCGGGCTGCCAGCTTTTCGGGGCCCCGA
GTCGCACCCAGCGAAGAGAGCGGGCCCCGGGACAAGCTCGAACTCCGGCCGCTCGCCC
TTCCCCGGCTCCGCTCCCTCTGCCCCCTCGGGGTGCGCGCGCCACGATGCTGCAGGGCC
CTGGCTCGCTGCTGCTGCTCTTCCTCGCCTCGCACTGCTGCCTGGGCTCGGCGCGCGGG
CTCTTCCTCTTTGGCCAGCCCCACTTCTCCTACAAGCGCAGCAATTGCAAGCCCATC
CCTGCCAACCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCTGCCAACCC
TGCTGGGCCACGAGACCATGAAGGAGGTGCTGGAGCAGGCCGCGCTTGGATCCCGCT
GGTCATGAAGCAGTGCCACCCGGACACCAAGAAGTTCCTGTGCTCGCTCTTCGCCCCC
GTCTGCCTCGATGACCTAGACGAGACCATCCAGCCATGCCACTCGCTCTGCGTGCAAGT
GAAGGACCGCTGCGCCCCGGTCATGTCCGCCTTCGGCTTCCCCTGGCCCCGACATGCTTG
AGTGCGACCGTTTCCCCCAGGACAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCA
CCTCCTGCCAGCCACCGAGGAAGCTCCAAAGGTATGTGAAGCCTGCAAAAATAAAAAT
GATGATGACAACGACATAATGGAAACGCTTTGTAAAAATGATTTTGCCTGAAAATAA
AAGTGAAGGAGATAACCTACATCAACCGAGATACCAAAATCATCCTGGAGACCAAGA

GCAAGACCATTACAAAGCTGAACGGTGTGTCCGAAAGGGACCTGAAGAAATCGGTGCT
GTGGCTCAAAGACAGCTTGCAGTGCACCTGTGAGGAGATGAACGACATCAACGCGCCC
TATCTGGTCATGGGACAGAAACAGGGTGGGGAGCTGGTGATCACCTCGGTGAAGCGGT
GGCAGAAGGGGCAGAGAGAGTTCAAGCGCATCTCCCGCAGCATCCGCAAGCTGCAGT
GCTAGTCCCGGCATCCTGATGGCTCCGACAGGCCTGCTCCAGAGCACGGCTGACCATT
CTGCTCCGGGATCTCAGCTCCCGTTCCTCAAGCACACTCCTAGCTGCTCCAGTCTCAGC
CTGGGCAGCTTCCCCCTGCCTTTTGCACGTTTGCATCCCCAGCATTTCTGAGTTATAAG
GCCACAGGAGTGGATAGCTGTTTTACCTAAAGGAAAAGCCCACCCGA
ATCTTGTAGAAATATTCAAACATAATAAATCATGAATATTTTATGAAGTTT

Figure 82

MLQPGSLLLFLASHCCLGSARGLFLFGQPDFSYKRSNCKPIPANLQLCHGIEYQNMRLP
NLLGHETMKEVLEQAGAWPLVMKQCHPDTKKFLCSLFAPVCLDDLDETIQPSHSLCVQV
KDRCAPVMSAFGFPWPDMLECDRFPQDNDLCIPLASSDHLLPATEEAPKVCEACKNKND
DNDIMETLCKNDFALKIKVKEITYINRDTKIILETKSKTIYKLNQVSRDLKKSVLWLKDSL
QCTCEEMNDINAPYLVMGQKQGGELVITSVKRWQKGQREFKRISRSIRKLQC

Figure 83

ACGGGGCCTGGGCGGSAGGGGCGGTGGCTGGAGCTCGGTAAAGCTCGTGGGACCCCAT
TGGGGGAATTTGATCCAAGGAAGCGGTGATTGCCGGGGGAGGAGAAGCTCCCAGATCC
TTGTGTCCACTTGCAGCGGGGGAGGCGGAGACGCGGAGCGGGCCTTTTGGCGTCCACT
GCGCGGTGCACCCTGCCCCATCCTGCCGGGATCATGGTCTGCGGCAGCCCGGGAGGG
ATGCTGCTGCTGCGGGCGGGCTGCTTGCCCTGGCTGCTCTCTGCCTGCTCCGGGTGCC
CGGGGCTCGGGCTGCAGCCTGTGAGCCCCTCCGCATCCCCCTGTGCAAGTCCCTGCCCT
GGAACATGACTAAGATGCCCAACCACCTGCACCACAGCACTCAGGCCAACGCCATCCT
GGCCATCGAGCAGTTCGAAGGTCTGCTGGGCACCCACTGCAGCCCCGATCTGCTCTTCT
TCCTCTGTGCCATGTACGCGCCCATCTGCACCATTTGACTTCCAGCACGAGCCCATCAAC
CCCTGTAAGTCTGTGTGCGAGCGGGCCCGGCAGGGCTGTGAGCCCATACTCATCAAGT
ACCGCCACTCGTGGCCGGAGAACCTGGCCTGCGAGGAGCTGCCAGTGTACGACAGGGG
CGTGTGCATCTCTCCCGAGGCCATCGTTACTGCGGACGGAGCTGATTTTCTATGGATT
CTAGTAACGGAACTGTAGAGGGGCAAGCAGTGAACGCTGTAAATGTAAGCCTATTAG
AGCTACACAGAAGACCTATTTCCGGAACAATTACAACATATGTCATTCGGGCTAAAGTT
AAAGAGATAAAGACTAAGTGCCATGATGTGACTGCAGTAGTGGAGGTGAAGGAGATT
CTAAAGTCCTCTCTGGTAAACATTCCACGGGACACTGTCAACCTCTATACCAGCTCTGG
CTGCCTCTGCCCTCCACTTAATGTTAATGAGGAATATATCATCATGGGCTATGAAGATG
AGGAACGTTCCAGATTACTCTTGGTGGAAAGGCTCTATAGCTGAGAAGTGGAAGGATCG
ACTCGGTAAAAAAGTTAAGCGCTGGGATATGAAGCTTCGTCATCTTGGACTCAGTAAA
AGTGATTCTAGCAATAGTGATTCCACTCAGAGTCAGAAGTCTGGCAGGAACCTCGAACC
CCCGGCAAGCACGCAACTAAATCCCGAAATACAAAAAGTAACACAGTGGACTTCCTAT
TAAGACTTACTTGCTGCTGGACTAGCAAAGGAAAATTGCACTATTGCACATCATATT
CTATTGTTTACTATAAAAATCATGTGATAACTGATTATTACTTCTGTTTCTCTTTGGTTT
CTGCTTCTCTTCTCTCAACCCCTTTGTAATGGTTTGGGGGCAGACTCTTAAGTATATT
GTGAGTTTTCTATTTCACTAATCATGAGAAAACTGTTCTTTTGAATAATAATAAATT
AAACATGCTGTTA

Figure 84

MVCGSPGGMLLLRAGLLALAALCLLRVPGARAAACEPVRIPLCKSLPWNMTKMPNHLHH
 STQANAILAIEQFEGLLGTHCSPDLLFFLCAMYAPICTIDFQHEPIKPCKSV CERARQGCEPIL
 IKYRHSWPENLACEELPVYDRGVCISPEAIVTADGADFPMDSSNGNCRGASSERCKCKPIR
 ATQKTYFRNNYNYVIRAKVKEIKTKCHDVTAVVEVKEILKSSLVNIPRDTVNL YTSSGCLC
 PPLNVNEEYIIMGYEDEERSRLLLVEGSIAEKWKDRLGKKVKRWDMKLRHLGLSKSDSSN
 SDSTQSQKSGRNSNPRQARN

Figure 85

CAGCGGCCGCTGAATTCTAGGGCGGGTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGC
 TCGTGCCCTGTGTGCCAGACGGCGGAGCTCCGCGGCCGGAACCCGCGGCCCGCTTTG
 CTGCCGACTGGAGTTTGGGGGAAGAACTCTCCTGCGCCCCAGAAGATTTCTTCCTCGG
 CGAAGGGACAGCGAAAGATGAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCCGG
 GGTCGCAGCGCGAGAGGGCAGTGCCATGTTCTCTCCATCCTAGTGGCGCTGTGCCTGT
 GGCTGCACCTGGCGCTGGGCGTGCGCGGCGCGCCCTGCGAGGCGGTGCGCATCCCTAT
 GTGCCGGCACATGCCCTGGAACATCACGCGGATGCCCAACCACCTGCACCACAGCACG
 CAGGAGAACGCCATCCTGGCCATCGAGCAGTACGAGGAGCTGGTGGACGTGAACTGC
 AGCGCCGTGCTGCGCTTCTTCTTCTGTGCCATGTACGCGCCCATTTGCACCCTGGAGTT
 CCTGCACGACCCTATCAAGCCGTGCAAGTCGGTGTGCCAACGCGCGCGCGACGACTGC
 GAGCCCCCTCATGAAGATGTACAACCACAGCTGGCCCCGAAAGCCTGGCCTGCGACGAGC
 TGCCTGTCTATGACCGTGGCGTGTGCATTTGCGCTGAAGCCATCGTCACGGACCTCCCG
 GAGGATGTAAAGTGGATAGACATCACACCAGACATGATGGTACAGGAAAGGCCTCTTG
 ATGTTGACTGTAAACGCCTAAGCCCCGATCGGTGCAAGTGTA AAAAGGTGAAGCCAAC
 TTTGGCAACGTATCTCAGCAAAAACCTACAGCTATGTTATTCATGCCAAAATAAAAGCTG
 TGCAGAGGAGTGGCTGCAATGAGGTCACAACGGTGGTGGATGTAAAAGAGATCTTCAA
 GTCCTCATCACCCATCCCTCGAACTCAAGTCCCGCTCATTACAAATTCTTCTTGCCAGT
 GTCCACACATCCTGCCCCATCAAGATGTTCTCATCATGTGTTACGAGTGGCGTTCAAGG
 ATGATGCTTCTTGAAAATTGCTTAGTTGAAAAATGGAGAGATCAGCTTAGTAAAAGAT
 CCATACAGTGGGAAGAGAGGGCTGCAGGAACAGCGGAGAACAGTTCAGGACAAGAAGA
 AAACAGCCGGGCGCACCCAGTCGTAGTAATCCCCCAAACCAAAGGGAAAGCCTCCTGC
 TCCCAAACCAGCCAGTCCCAAGAAGAACATTA AAAACTAGGAGTGCCCAAGAGAAAC
 AAACCCGAAAAGAGTGTGAGCTAACTAGTTTCCAAAGCGGAGACTTCCGACTTCCTTA
 CAGGATGAGGCTGGGCATTGCCTGGGACAGCCTATGTAAGGCCATGTGCCCTTGCCC
 TAACAACCTCACTGCAGTGCTCTTCATAGACACATCTTGACGATTTTTCTTAAGGCTAT
 GCTTCAGTTTTTCTTTGTAAGCCATCACAAGCCATAGTGGTAGGTTTGCCCTTTGGTACA
 GAAGGTGAGTTAAAGCTGGTGGAAAAGGCTTATTGCATTGCATTACAGGTAACCTGTG
 TGCATACTCTAGAAGAGTAGGGAAAATAATGCTTGTTACAATTGACCTAATATGTGC
 ATTGTAAAATAAAATGCCATATTTCAAACAAAACACGTAATTTTTTTACAGTATGTTTA
 TTACCTTTTGATATCTGTTGTTGCAATGTTAGTGATGTTTTAAATGTGATGAAAATATA
 ATGTTTTTAAGAAGGAACAGTAGTGGAATGAATGTTAAAAGATCTTTATGTGTTTATGG
 TCTGCAGAAGGATTTTTGTGATGAAAGGGGATTTTTTGAAAAATTAGAGAAGTAGCAT
 ATGGAAAATTATAATGTGTTTTTTTACCAATGACTTCAGTTTCTGTTTTTAGCTAGAAAC
 TAAAAACAAAAATAATAAAGAAAAATAAATAAAAAAGGAGAGGCAGACAATGTC
 TGGATTCTGTTTTTTGGTTACCTGATTTCCATGATCATGATGCTTCTTGTC AACACCCCT
 CTTAAGCAGCACCAGAAACAGTGAGTTTGTCTGTACCATTAGGAGTTAGGTACTAATTA
 GTTGGCTAATGCTCAAGTATTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTC
 CCAGGACATCCACCCTGAGAATAATTTGACAAGCTTAAAAATGGCCTTCATGTGAGTG
 CCAAATTTTGTTTTTCTTCATTAAATATTTTCTTTGCCTAAATACATGTGAGAGGAGTT
 AAATATAAATGTACAGAGAGGAAAGTTGAGTTCACCTCTGAAATGAGAATTACTTGA
 CAGTTGGGATACTTTAATCAGAAAAAAGAACTTATTTGCAGCATTTTATCAACAAATT
 TCATAATTGTGGACAATTGGAGGCATTTATTTTAAAAACAATTTTATTGGCCTTTTGCT

AACACAGTAAGCATGTATTTTATAAGGCATTCAATAAATGCACAACGCCCAAAGGAAA
TAAAATCCTATCTAATCCTACTCTCCACTACACAGAGGTAATCACTATTAGTATTTTGG
CATATTATTCTCCAGGTGTTTGCTTATGCACTTATAAAATGATTTGAACAAATAAAACT
AGGAACCTGTATACATGTGTTTCATAACCTGCCTCCTTTGCTTGGCCCTTTATTGAGATA
AGTTTTCTGTCAAGAAAGCAGAAACCATCTCATTTCTAACAGCTGTGTTATATTCCAT
AGTATGCATTACTCAACAAACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGA
CAATACTGAATAAACATCTCACCGGAATTC

Figure 86

MFLSILVALCLWLHLALGVRGAPCEAVRIPMCRHMPWNITRMPNHLHHSTQENAILAIEQY
EELVDVNCSAVLRFFLCAMYAPICTLEFLHDPKPKSVQCQRARDDCEPLMKMYNHSWPE
SLACDELPVYDRGVCISPEAIVTDLPEDEVKVIDITPDMMVQERPLDVDCRKLSPDRCKCKK
VKPTLATYLSKNYSYVIHAKIKAVQRS GCNEVTTVDVKEIFKSSSPIPRTQVPLITNSSCQC
PHILPHQDVLIMCYEWRSRMMLLENCLVEKWRDQLSKRSIQWEERLQEQRRRTVQDKKKT
AGRTSRSNPPKPKGKPPAPKPASPCKNIKTRSAQKRTNPKRV

Figure 87

AAGCTTGATATCGAATTCGCGGCCGCGTCGACGGGAGGCGCCAGGATCAGTCGGGGCA
CCCGCAGCGCAGGCTGCCACCCACCTGGGCGACCTCCGCGGCGGCGGCGGCGGCGGCT
GGGTAGAGTCAGGGCCGGGGGCGCACGCCGAACACCTGGGCGCGCGGGCACCGAGC
GTCGGGGGGCTGCGCGGCGCGACCCCTGGAGAGGGCGCAGCCGATGCGGGCGGCGGCG
GCGGCGGGGGGCGTGCGGACGGCCGCGCTGGCGCTGCTGCTGGGGGCGCTGCACTGG
GCGCCGGCGCGCTGCGAGGAGTACGACTACTATGGCTGGCAGGCCGAGCCGCTGCACG
GCCGCTCCTACTCCAAGCCGCCGAGTGCCTTGACATCCCTGCCGACCTGCCGCTCTGC
CACACGGTGGGCTACAAGCGCATGCGGCTGCCAACCTGCTGGAGCACGAGAGCCTGG
CCGAAGTGAAGCAGCAGGCGAGCAGCTGGCTGCCGCTGCTGGCCAAGCGCTGCCACTC
GGATACGCAGGTCTTCCTGTGCTCGCTCTTTGCGCCCGTCTGTCTCGACCGGCCCATCT
ACCCGTGCCGCTCGCTGTGCGAGGCCGTGCGCGCCGGCTGCGCGCCGCTCATGGAGGC
CTACGGCTTCCCCTGGCCTGAGATGCTGCACTGCCACAAGTTCCCCCTGGACAACGACC
TCTGCATCGCCGTGCAGTTCGGGCACCTGCCCGCCACCGCGCCTCCAGTGACCAAGATC
TGCGCCCAGTGTGAGATGGAGCACAGTGCTGACGGCCTCATGGAGCAGATGTGCTCCA
GTGACTTTGTGGTCAAAATGCGCATCAAGGAGATCAAGATAGAGAATGGGGACCGGA
AGCTGATTGGAGCCCAGAAAAAGAAGAAGCTGCTCAAGCCGGGCCCCCTGAAGCGCA
AGGACACCAAGCGGCTGGTGCTGCACATGAAGAATGGCGCGGGCTGCCCTGCCACA
GCTGGACAGCCTGGCGGGCAGCTTCCTGGTTCATGGGCGGCAAAGTGGATGGACAGCTG
CTGCTCATGGCCGTCTACCGCTGGGACAAGAAGAATAAGGAGATGAAGTTTGCAGTCA
AATTCATGTTCTCCTACCCCTGCTCCCTCTACTACCCTTTCTTCTACGGGGCGGCAGAGC
CCCACTGAAGGGCACTCCTCCTTGCCCTGCCAGCTGTGCCTTGCTTGCCCTCTGGCCCC
GCCCCAACTTCCAGGCTGACCCGGCCCTACTGGAGGGTGTTTTACGAATGTTGTTACT
GGCACAAGGCCTAAGGGATGGGCACGGAGCCAGGCTGTCCTTTTTGACCCAGGGGTC
CTGGGGTCCCTGGGATGTTGGGCTTCCTCTCTCAGGAGCAGGGCTTCTTCATCTGGGTG
AAGACCTCAGGGTCTCAGAAAGTAGGCAGGGGAGGAGAGGGTAAGGGAAAGGTGGAG
GGGCTCAGGGCACCTGAGGCGGAGGTTTCAGAGTAGAAGGTGATGTCAGCTCCAGCT
CCCCTCTGTCGGTGGTGGGGCCTCACCTTGAAGAGGGAAGTCTCAATATTAGGCTAAG
CTATTTGGGAAAGTTCTCCCCACCGCCCCCTGTACGCGTCATCCTAGCCCCCTTAGGAA
AGGAGTTAGGGTCTCAGTGCTCCAGCCACACCCCCCTGCCTTCCCCAGCTTGCCCATTT
CCCTGCCCAAGGCCAGAGCTCCCCCAGACTGGAGAGCAAGCCCAGCCCAGCCTCG
GCATAGACCCCCCTTCTGGTCCGCCCCGTGGCTCGATTCCCGGGATTCAATCCTCAGCCTC

TGCTTCTCCCTTTTATCCCAATAAGTTATTGCTACTGCTGTGAGGCCATAGGTACTAGAC
AACCAATACATGCAGGGTTGGGTTTTCTAATTTTTTAACTTTTTAATTAAATCAAAGGT
CGACGCGCGGCCGCGGAATTCCTGCAGCCCGGGGGATCCCCGGGTACCGAGCTCGAAT
TC

Figure 88

TEILPALCVLIHHTDVNILDVTVWALSYLTDAGNEQIQMVIDSGIVPHLVPLLSHQEVKVQT
AALRAVGNIIVTGTDEQTQVVLNCDALSHFPALLTHPKEKINKEAVWFLSNITAGNQQQVQ
AVIDANLVPMIHLLDKGDFGTQKEAAWAISNLTISGRKDQVAYLIQQNVIPFCNLLTVKD
AQVVQVVL DGLSNILKMAEDEAETIGNLIEECGLEKIEQLQNHENEDIYKLAYEIIDQFFSS
DDIDEDPSLVPEAIQGGTGFNSSANVPTEGFQF

Figure 89

ATGCATCTCCTCTTATTTTCAGCTGCTGGTACTCCTGCCTCTAGGAAAGACCACACGGCA
CCAGGATGGCCGCCAGAATCAGAGTTCTCTTTCCCCCGTACTCCTGCCAAGGAATCAA
AGAGAGCTTCCCACAGGCAACCATGAGGAAGCTGAGGAGAAGCCAGATCTGTTTGTGCG
CAGTGCCACACCTTGTAGCCACCAGCCCTGCAGGGGAAGGCCAGAGGCAGAGAGAGA
AGATGCTGTCCAGATTTGGCAGGTTCTGGAAGAAGCCTGAGAGAGAAATGCATCCATC
CAGGGACTCAGATAGTGAGCCCTTCCCACCTGGGACCCAGTCCCTCATCCAGCCGATA
GATGGAATGAAAATGGAGAAATCTCCTCTTCGGGAAGAAGCCAAGAAATTCTGGCACC
ACTTCATGTTTCAGAAAACTCCGGCTTCTCAGGGGGTTCATCTTGCCCATCAAAGCCAT
GAAGTACATTGGGAGACCTGCAGGACAGTGCCCTTCAGCCAGACTATAACCCACGAAG
GCTGTGAAAAAGTAGTTGTTTCAGAACACCTTTGCTTTGGGAAATGCGGGTCTGTTTCAT
TTTCTGAGCCGCGCAGCACTCCCATACTCCTGCTCTCACTGTTTGCCCTGCCAAGTTC
ACCACGATGCACTTGCCACTGAACTGCACTGAACTTTCTCCGTGATCAAGGTGGTGAT
GCTGGTGGAGGAGTGCCAGTGCAAGGTGAAGACGGAGCATGAAGATGGACACATCCT
ACATGCTGGCTCCAGGATTCTTTATCCCAGGAGTTTCAGCTTGA

Figure 90

MHLLLFQLLVLLPLGKTRHQDGRQNQSSLSPVLLPRNQRELPTGNHEEAEEKPDLFVAVP
HLVATSPAGEGQRQREKMLSRFGRFWKKPEREMHPSRSDSEPFPPGTQSLIQPIDGMKME
KSPLREEAKKFWHHFMFRKTPASQGVILPIKSHEVHWETCRTVPFSQTITHEGCEKVVVQN
NLFCGKCGSVHFPGAQAHSHTSCSHCLPAKFTTMHLPLNCTELSSVIKVVMLVEECQCKV
KTEHEDGHILHAGSQDSFIPGVSA

Figure 91

CGGCACGGTTTCGTGGGGACCCAGGCTTGCAAAGTGACGGTCATTTTCTCTTTCTTTCT
CCCTCTTGAGTCCTTCTGAGATGATGGCTCTGGGCGCAGCGGGAGCTACCCGGGTCTTT
GTCGCGATGGTAGCGGCGGCTCTCGGCGGCCACCCTCTGCTGGGAGTGAGCGCCACCT
TGAACCTCGTTCTCAATTCCAACGCTATCAAGAACCTGCCCCACCGCTGGGCGGCGCT
GCGGGGCACCCAGGCTCTGCAGTCAGCGCCGCGCCGGGAATCCTGTACCCGGGCGGGA
ATAAGTACCAGACCATTGACAACTACCAGCCGTACCCGTGCGCAGAGGACGAGGAGTG
CGGCACTGATGAGTACTGCGCTAGTCCCACCCGCGGAGGGGACGCGAGGCGTGCAAATC
TGTCTCGCCTGCAGGAAGCGCCGAAAACGCTGCATGCGTCACGCTATGTGCTGCCCCG

GGAATTACTGCAAAAATGGAATATGTGTGTCTTCTGATCAAAAATCATTTCGAGGAGA
AATTGAGGAAACCATCACTGAAAGCTTTGGTAATGATCATAGCACCTTGGATGGGTAT
TCCAGAAGAACCACCTTGTCTTCAAAAATGTATCACACCAAAGGACAAGAAGGTTCTG
TTTGTCTCCGGTCATCAGACTGTGCCTCAGGATTGTGTTGTGCTAGACACTTCTGGTCCA
AGATCTGTAAACCTGTCCTGAAAGAAGGTCAAGTGTGTACCAAGCATAGGAGAAAAGG
CTCTCATGGACTAGAAATATTCCAGCGTTGTTACTGTGGAGAAGGTCTGTCTTGCCGGA
TACAGAAAGATCACCATCAAGCCAGTAATTCTTCTAGGCTTCACACTTGTGAGAGACAC
TAAACCAGCTATCCAAATGCAGTGAACCTCTTTATATAATAGATGCTATGAAAACCTT
TTATGACCTTCATCAACTCAATCCTAAGGATATACAAGTTCTGTGGTTTCAGTTAAGCA
TTCCAATAACACCTTCCAAAAACCTGGAGTGTAAGAGCTTTGTTTCTTTATGGAACCTC
CCTGTGATTGCAGTAAATTACTGTATTGTAAATTCTCAGTGTGGCACTTACCTGTAAAT
GCAATGAAACTTTTAATTATTTTTCTAAAGGTGCTGCACTGCCTATTTTTCTCTTGTTA
TGTAATTTTTGTACACATTGATTGTTATCTTGACTGACAAATATTCTATATTGAACTGA
AGTAAATCATTTTCAGCTTATAGTTCTTAAAAGCATAACCCTTTACCCCATTTAATTCTAG
AGTCTAGAACGCAAGGATCTCTTGGAATGACAAATGATAGGTACCTAAAATGTAAACAT
GAAAATACTAGCTTATTTTCTGAAATGTACTATCTTAATGCTTAAATTATTTCCCTTT
AGGCTGTGATAGTTTTTGAAATAAAATTTAACATTTAATATCATGAAATGTTATAAGTA
GACAT

Figure 92

MMALGAAGATRVFVAMVAAALGGHPLLGVSATLNSVLNSNAIKNLPPLGGAAGHPGSA
VSAAPGILYPGGNKYQTIDNYQPYPCAEDEECGTDEYCASPTRGGDAGVQICLACRKRK
RCMRHAMCCPGNYCKNGICVSSDQNHFRGEIETITESFGNDHSTLDGYSRRTLSSKMYH
TKGQEGSVCLRSSDCASGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCG
EGLSCRIQKDDHHQASNSSLHTCQRH

Figure 93

GCGGGTCTCGCTTGGGTTCGCTAATTTCTGTCCTGAGGCGTGAGACTGAGTTCATAGG
GTCCTGGGTCCCCGAACCAGGAAGGGTTGAGGGAACACAATCTGCAAGCCCCCGCGAC
CCAAGTGAGGGGCCCCGTGTTGGGGTCCTCCCTCCCTTTGCATTCCCACCCCTCCGGGC
TTTGCGTCTTCTGGGGACCCCTCGCCGGGAGATGGCCGCGTTGATGCGGAGCAAGG
ATTCGTCCTGCTGCCTGCTCCTACTGGCCGCGGTGCTGATGGTGGAGAGCTCACAGATC
GGCAGTTCGCGGGCCAAACTCAACTCCATCAAGTCCTCTCTGGGCGGGGAGACGCCTG
GTCAGGCCGCCAATCGATCTGCGGGCATGTACCAAGGACTGGCATTGCGCGGCAGTAA
GAAGGGCAAAAACCTGGGGCAGGCCTACCCTTGAGCAGTGATAAGGAGTGTGAAGTT
GGGAGGTATTGCCACAGTCCCCACCAAGGATCATCGGCCTGCATGGTGTGTCGGAGAA
AAAAGAAGCGCTGCCACCGAGATGGCATGTGCTGCCCCAGTACCCGCTGCAATAATGG
CATCTGTATCCCAGTTACTGAAAGCATCTTAACCCCTCACATCCCGGCTCTGGATGGTA
CTCGGCACAGAGATCGAAACCACGGTCATTACTCAAACCATGACTTGGGATGGCAGAA
TCTAGGAAGACCACACACTAAGATGTCACATATAAAAGGGCATGAAGGAGACCCCTGC
CTACGATCATCAGACTGCATTGAAGGGTTTTGCTGTGCTCGTCATTTCTGGACCAAAAT
CTGCAAACCAGTGCTCCATCAGGGGGAAGTCTGTACCAAACAACGCAAGAAGGGTTCT
CATGGGCTGGAAATTTTCCAGCGTTGCGACTGTGCGAAGGGCCTGTCTTGCAAAGTATG
GAAAGATGCCACCTACTCCTCCAAAGCCAGACTCCATGTGTGTCAGAAAATTTGATCA
CCATTGAGGAACATCATCAATTGCAGACTGTGAAGTTGTGTATTTAATGCATTATAGCA
TGGTGGAAAATAAGGTTTCAGATGCAGAAGAATGGCTAAAATAAGAAACGTGATAAGA
ATATAGATGATCAC

Figure 94

MAALMRSKDSSCCLLLLA AVL MVES SQIGSSRAKLNSIKSSLGGETPGQAANRSAGMYQG
LAFGGSKKGKNLGQAYPCSSDKECEVGRYCHSPHQGSSACMVCRRKKKRCHRDGMCCPS
TRCNNGICIPVTESILTPHIPALDGT RHRDRNHGHYSNHD LGWQNLGRPHTKMSHIKGHEG
DPCLRSSDCIEGFCCARHFWTKICKPVLHQGEVCTKQRKKGSHGLEIFQRCDCAKGLSCKV
WKDATYSSKARLHVCQKI

Figure 95

CTATCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCCATGTGCAC
CGAGAAATTCACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTTCAGAGACAG
TTATCACATCTGTGGGAGACGAAGAAGGCAGAAGGAGCCACGAGTGCATCATCGACG
AGGACTGTGGGCCCAGCATGTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGCC
ATGCCGGGGCCAGAGGATGCTCTGCACCCGGGACAGTGAGTGCTGTGGAGACCAGCTG
TGTGTCTGGGGTCACTGCACCAAAATGGCCACCAGGGGCAGCAATGGGACCATCTGTG
ACAACCAGAGGGACTGCCAGCCGGGGCTGTGCTGTGCCTTCCAGAGAGGCCTGCTGTT
CCCTGTGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCCATGACCCCGCCAGCCGG
CTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGACCGATGCCCTTG
TGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGTGCAAGCCG
ACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCCAGAGAGGTCCCCG
ATGAGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGA
GAGGAGCCTGACTGAAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTG
CTGGGAGGGGAAGAGATTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAAT
AGCTAATTTATTTCCCCAGGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCCTAC
ATCTTCTTCCAGTAAGTTTCCCCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTC
AGCTCCCCCAGGCTGTTCTCCAGGCTTCACAGTCTGGTGCTTGGGAGAGTCAGGCAGG
GTTAAACTGCAGGAGCAGTTTGCCACCCCTGTCCAGATTATTGGCTGCTTTGCCTCTAC
CAGTTGGCAGACAGCCGTTTGTCTACATGGCTTTGATAATTGTTTGAGGGGAGGAGAT
GGAAACAATGTGGAGTCTCCCTCTGATTGGTTTTGGGGAAATGTGGAGAAGAGTGCCC
TGCTTTGCAAACATCAACCTGGCAAAAATGCAACAAATGAATTTTCCACGCAGTTCTTT
CCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCAGATGAAATGTTCTGTTACCCCT
GCATTACATGTGTTTATTCATCCAGCAGTGTTGCTCAGCTCCTACCTCTGTGCCAGGGC
AGCATTTTCATATCCAAGATCAATTCCTCTCTCAGCACAGCCTGGGGAGGGGGTCATT
GTTCTCCTCGTCCATCAGGGATCTCAGAGGNCTCAGAGACTGCAAGCTGCTTGCCCAA
GTCACACAGCTAGTGAAGACCAGAGCAGTTTCATCTGGTTGTGACTCTAAGCTCAGTGC
TCTCTCCACTACCCACACACCAGCCTTGGTGCCACCAAAAGTGCTCCCCAAAAGGAAGG
AGAATGGGATTTTTCTTTTGAGGCATGCACATCTGGAATTAAGGTCAAACCTAATTCTCA
CATCCCTCTAAAAGTAACTACTGTTAGGAACAGCAGTGTTCTCACAGTGTGGGGCAG
CCGTCCTTCTAATGAAGACAATGATATTGACACTGTCCCTCTTTGGCAGTTGCATTAGT
AACTTTGAAAGGTATATGACTGAGCGTAGCATAACAGGTTAACCTGCAGAAACAGTACT
TAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCAAAATCACTTAGCAGCAACT
GAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAGCAGGGCTGTGTGAAACAT
GGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTCCACAAATGATGTTTTCA
GGTGTGATGAGTGTGTCACCATGTATTTCATCCAGAGTTCTTAAAGTTTAAAGTTGCA
CATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAAACATAAGTTGCATT
TAGAAATCAAGCATAAATCAC

Figure 96

MQRLGATLLCLLLAAAVPTAPAPAPTATSAPVKPGPALSYQEEATLNEMFREVEELMEDT
QHKLRS AVEEMEAEEAAAKASSEVNLANLPPSYHNETNTDTKVGNNTIHVHREIHKITNNQ
TGQMV FSETVITSVGDEEGRRSHECIIDEDCGPSMYCQFASFQYTCQPCR GQRM LCTR DSE
CCGDQLCVWGHCTKMATRGSNGTICDNQRDCQPGLCCAFQRGLLPVCTPLPVEGELCHD
PASRLDLITWELEPDGALDRCPCASGLLCQPHSHSLVYVCKPTFVGSRDQDGEILLPREVP
DEYEVGSFMEEVRQELEDLERSLTEEMALGEPAAAAAALLGGEI

Figure 97

AGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGAGCAGCCT
CGCTTTGGTGACGCACAGTGCTGGGACCCTCCAGGAGCCCCGGGATTGAAGGATGGTG
GCGGCCGTCTGCTGGGGCTGAGCTGGCTCTGCTCTCCCCTGGGAGCTCTGGTCCTGGA
CTTCAACAACATCAGGAGCTCTGCTGACCTGCATGGGGCCCCGGAAGGGCTCACAGTGC
CTGTCTGACACGGACTGCAATACCAGAAAGTTCTGCCTCCAGCCCCGCGATGAGAAGC
CGTTCTGTGCTACATGTCGTGGGTTGCGGAGGAGGTGCCAGCGAGATGCCATGTGCTG
CCCTGGGACACTCTGTGTGAACGATGTTTGTACTACGATGGAAGATGCAACCCCAATAT
TAGAAAGGCAGCTTGATGAGCAAGATGGCACACATGCAGAAGGAACAACCTGGGCACC
CAGTCCAGGAAAACCAACCCAAAAGGAAGCCAAGTATTAAGAAATCACAAGGCAGGA
AGGGACAAGAGGGAGAAAGTTGTCTGAGAACTTTTGAAGTGTGGCCCTGGACTTTGCTG
TGCTCGTCATTTTTGGACGAAAATTTGTAAGCCAGTCCTTTTGGAGGGACAGGTCTGCT
CCAGAAGAGGGCATAAAGACACTGCTCAAGCTCCAGAAATCTTCCAGCGTTGCGACTG
TGGCCCTGGACTACTGTGTCGAAGCCAATTGACCAGCAATCGGCAGCATGCTCGATTA
AGAGTATGCCAAAAAATAGAAAAGCTATAAATATTTCAAAATAAAGAAGAATCCACAT
TGC

Figure 98

MVA AVLGLSWLCSPLGALVLD FNNIRSSADLHGARKGSQCLSDTDCNTRKFCLQPRDEK
PFCATCRGLRRRCQRDAMCCPGTLCVNDVCTTMEDATPILERQLDEQDGT HAEGTTGHPV
QENQPKRKPSIKKSQGRKGQEGESCLRTFDCGPGLCCARHFWTKICKPVLLGQVCSRRGH
KDTAQAP EIFQRCD CGPGLLCRSQLTSNRQHARLRVCQKIEKL

Figure 99

AGGCAGAATACTTCTATGAATTCCTGTCCTTGCGCTCCCTGGATAAAGGCATCATGGCA
GATCCAACCGTCAATGTCCCTCTGCTGGGAACAGTGCCTCACAAGGCATCAGTTGTTCA
AGTTGGTTTCCCATGTCTTGGAACACAGGATGGGGTGGCAGCATTGAAAGTGATGTG
ATTGTTATGAATTCTGAAGGCAACACCATTCTCAAACACCTCAAAATGCTATCTTCTT
TAAAACATGTCAACAAGCTGAGTGCCAGGCGGGTGCCGAAATGGAGGGCTTTTGTAAT
GAAAGACGCATCTGCGAGTGTCTGATGGGTTCACGGACCTCACTGTGAGAAAGCCC
TTTGTACCCACGATGTATGAATGGTGGACTTTGTGTGACTCCTGGTTTCTGCATCTGCC
CACCTGGATTCTATGGAGTGAAGTGTGACAAAGCAAAGTCTCAACCACCTGCTTTAAT
GGAGGGACCTGTTTCTACCCTGGAAAATGTATTTGCCCTCCAGGACTAGAGGGAGAGC

AGTGTGAAATCAGCAAATGCCACAACCTGTGCGAAATGGAGGTAAATGCATTGGTAA
AAGCAAATGTAAGTGTTCCAAAGGTTACCAGGGAGACCTCTGTTCAAAGCCTGTCTGC
GAGCCTGGCTGTGGTGCACATGGAACCTGCCATGAACCCAACAAATGCCAATGTCAAG
AAGGTTGGCATGGAAGACACTGCAATAAAAGGTACGAAGCCAGCCTCATACATGCCCT
GAGCGCAGCAGCGCCAGCTCAGGCAGCACACGCCTTCACTTAAAAAGGCCGAGGAG
CGGCGGCATCCACCTGAATCCAATTACATCTGGTGAACCTCCGACATCTGAAACGTTTTA
AGTTACACCAAGTTCATAGCCTTTGTTAACCTTTCATGTGTTGAATGTTCAAATAATGTT
CATTACACTTAAGAATACTGGCCTGAATTTTATTAGCTTCATTATAAATCACTGAGCTG
ATATTTACTCTTCCTTTTAAGTTTTCTAAGTACGTCTGTAGCATGATGGTATAGATTTTC
TTGTTTCAGTGCTTTGGGACAGATTTTATATTATGTCAATTGATCAGGTTAAAATTTTCA
GTGTGTAGTTGGCAGATATTTTCAAATTACAATGCATTTATGGTGTCTGGGGGCAGGG
GAACATCAGAAAGGTTAAATTGGGCAAAAATGCGTAAGTCACAAGAATTGGATGGTG
CAGTTAATGTTGAAGTTACAGCATTTTCAATTTTATTGTCAGATATTTAGATGTTTGTTA
CATTTTAAAAATTGCTCTTAATTTTTAACTCTCAATACAATATATTTTGACCTTACCA
TTATTCAGAGATTCAGTATTAATAAAAAAAAAAATTACACTGTGGTAGTGGCATTAA
ACAATATAATATATTCTAAACACAATGAAATAGGGAATATAATGTATGAACTTTTTGCA
TTGGCTTGAAGCAATATAATATATTGTAAACAAAACACAGCTCTTACCTAATAAACATT
TTATACTGTTTGTATGTATAAAATAAAGGTGCTGCTTTAGTTTTTC

Figure 100

MARRSAFPAAALWLWSILLCLLALRAEAGPPQEESLYLWIDAHQARVLIGFEEDILIVSEGK
MAPFTHDFRKAQQRMPAIPVNIHSMNFTWQAAGQAEYFYEFSLRSLDKGIMADPTVNVP
LLGTVPHKASVVQVGFPCLGKQDGVAAFEVDVIVMNSEGNTILQTPQNAIFFKTCLQAECP
GGCRNGGFCNERRICECPDGFHGPHEKALCTPRCMNGGLCVTPGFCICPPGFYGVNCDK
ANCS TTCFNGGT CFYPGKCICPPGLEGEQCEISKCPQPCRNGGKICGKSKCKCSKGYQGD
CSKPVCEPGCGAHGTCHEPNKCQCQEGWHGRHCNKRYEASLIHALR
PAGAQLRQHTPSLKKAEEERDPPESENITW

Figure 101

ATGGGCATCGGGCGCAGCGAGGGGGGCGCGCGGGGCAGCCCTGGGCGTGCTGCTG
GCGCTGGGCGCGGCGCTTCTGGCCGTGGGCTCGGCCAGCGAGTACGACTACGTGAGCT
TCCAGTCGGACATCGGCCCGTACCAGAGCGGGCGCTTCTACACCAAGCCACCTCAGTG
CGTGGACATCCCCGCGGACCTGCGGCTGTGCCACAACGTGGGCTACAAGAAGATGGTG
CTGCCAACCTGCTGGAGCACGAGACCATGGCGGAGGTGAAGCAGCAGGCCAGCAGC
TGGGTGCCCCCTGCTCAACAAGAACTGCCACGCCGGCACCCAGGTCTTCTCTGCTCGCT
CTTCGCGCCCGTCTGCCTGGACCGGCCCATCTACCCGTGTCGCTGGCTCTGCGAGGCCG
TGCGCGACTCGTGCGAGCCGGTCATGCAGTTCTTCGGCTTCTACTGGCCCGAGATGCTT
AAGTGTGACAAGTTCCCCGAGGGGGACGTCTGCATCGCCATGACGCCGCCCAATGCCA
CCGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCTCCTGTGACAACGAGTTGAA
ATCTGAGGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGGGCTGAGTTTAAAGATGA
TTGTGGGTAGCTCCATAACTCATGCTGCACGCTGGGTCCTTCTCATCCCAACTCCTCA
AAGCGGCAGGAGCAGGAACCTGGGGACTCCTGAGAGAAGGCTTGGATATGGCCTTTTAT
TACACTTCATCCAAGGAAATCTGCCCCCACCCTGTGCCAGGCCCGATCACGCATGAG
GCTAAAGACGGAGGCCACTCCGCTGGCTCTGGGTAGATCTGCCCTGGACTGTTTGCC
GACTGCCCGGAGCGCCCTCTGCCGGTCTGCAGCTTCCACACCACACGGAAGAAGTGG
GGAACTGAGGATACATTCTTCTCCTCCAGGTAAAGGGATTCTCAATGAAGGGCTTG
TGTGCACCTTCCACACTTAGATACCTCTACTACCTGAAAACCAGCATGCAGCATGTACA
TCAAGAGTACCAGGCACATAGTGCTCAAGTCTGGGCTAATATGCCACCTGCAGAGAGA
TGTAAGATGAAGAAGACAAAGCCATGTTTTCAAAGTGA

Figure 102

MGIGRSEGGRRGAALGVLLALGAALLAVGSASEYDYVSFQSDIGPYQSGRFYTKPPQCVDI
PADLRLCHNVGYKKMVLPNLLEHETMAEVKQQASSWVPLLKNKNCHAGTQVFLCSLFAPV
CLDRPIYPCRWLCEAVRDSCEPVMQFFGFYWPEMLKCDKFPEGDVCIAMTPPNATEASKP
QGTTVCPPCDNELKSEAIIEHLCASEFGLSLKMIVGSSHNSCCTLGPSHPNSSKRQEQLGTP
ERRLGYGLLLHFIQGNLPPCAQARSRLKTEATPLALGRSAPGLFADCPERPLPVCSFPH
HTEEVGKLRIHSFLLQVKGFSMKGLCAPSTLRYLYLKTSMQHVHQEYQAHS AQVWANM
PPAERCKDEEDKAMFSK

Figure 103

GGCGGGTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGCTCGTGCCCTGTGTGCCAGAC
GGCGGAGCTCCGCGGCCGACCCCGCGGCCCGCTTTGCTGCCGACTGGAGTTTGGGG
GAAGAACTCTCCTGCGCCCCAGAAGATTTCTTCTCCTCGGCGAAGGGACAGCGAAAGAT
GAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCCGGGGTCGCAGCGCGAGAGGGC
AGTGCCATGTTCTCTCCATCCTAGTGGCGCTGTGCCTGTGGCTGCACCTGGCGCTGGG
CGTGCGCGGCGCGCCCTGCGAGGCGGTGCGCATCCCTATGTGCCGGCACATGCCCTGG
AACATCACGCGGATGCCCAACCACTGCACCACAGCACGCAGGAGAACGCCATCCTGG
CCATCGAGCAGTACGAGGAGCTGGTGGACGTGAACTGCAGCGCCGTGCTGCGCTTCTT
CTTCTGTGCCATGTACGCGCCCATTTGCACCCTGGAGTTCCTGCACGACCCTATCAAGC
CGTGCAAGTCGGTGTGCCAACGCGCGCGCGACGACTGCGAGCCCCTCATGAAGATGTA
CAACCACAGCTGGCCCGAAAGCCTGGCCTGCGACGAGCTGCCTGTCTATGACCGTGGC
GTGTGCATTTGCGCTGAAGCCATCGTCACGGACCTCCCGGAGGATGTTAGTGGATAGA
CATCACACCAGACATGATGGTACAGGAAAGGCCTCTTGATGTTGACTGTAAACGCCTA
AGCCCCGATCGGTGCAAGTGTA AAAAGGTGAAGCCAACTTTGGCAACGTATCTCAGCA
AAA ACTACAGCTATGTTATTCATGCCAAAATAAAAGCTGTGCAGAGGAGTGGCTGCAA
TGAGGTCACAACGGTGGTGGATGTAAAAGAGATCTTCAAGTCCTCATCACCCATCCCTC
GAACTCAAGTCCCGCTCATTACAAATTCTTCTTGCCAGTGTCCACACATCCTGCCCCAT
CAAGATGTTCTCATCATGTGTACGAGTGGCGTTCAAGGATGATGCTTCTTGAAAATTG
CTTAGTTGAAAAATGGAGAGATCAGCTTAGTAAAAGATCCATACAGTGGGAAGAGAG
GCTGCAGGAACAGCGGAGAACAGTT CAGGACAAGAAGAAAACAGCCGGGCGCACCAG
TCGTAGTAATCCCCCAAACCAAAGGGAAAGCCTCCTGCTCCCAAACAGCCAGTCCC
AAGAAGAACATTAAACTAGGAGTGCC CAGAAGAGAACAACCCGAAAAGAGTGTGA
GCTAACTAGTTTCCAAAGCGGAGACTTCCGACTTCCTTACAGGATGAGGCTGGGCATTG
CCTGGGACAGCCTATGTAAAGGCCATGTGCCCTTGCCCTAACAACTCACTGCAGTGCTC
TTCATAGACACATCTTGCAGCATTTTTCTTAAGGCTATGCTTCAGTTTTTCTTTGTAAGC
CATCACAAGCCATAGTGGTAGGTTTGCCCTTTGGTACAGAAGGTGAGTTAAAGCTGGT
GGAAAAGGCTTATTGCATTGCATT CAGAGTAACCTGTGTGCATACTCTAGAAGAGTAG
GGAAAATAATGCTTGTTACAATTCGACCTAATATGTGCATTGTAAAATAAATGCCATAT
TTCAAACAAAACACGTAATTTTTTTACAGTATGTTTTATTACCTTTTGATATCTGTTGTT
GCAATGTTAGTGATGTTTTTAAATGTGATGAAAATATAATGTTTTTAAGAAGGAACAGT
AGTGGAATGAATGTTAAAAGATCTTTATGTGTTTATGGTCTGCAGAAGGATTTTTGTGA
TGAAAGGGGATTTTTTTGAAAAATTAGAGAAGTAGCATATGGAAAATTATAATGTGTTT
TTTTACCAATGACTTCAGTTTCTGTTTTTAGCTAGAACTTAAAAACAAAATAAATAAT
AAAGAAAATAAATAAAAAGGAGAGGCAGACAATGTCTGGATTCCCTGTTTTTTGGTTA

CCTGATTTCCATGATCATGATGCTTCTTGTCAACACCCTCTTAAGCAGCACCAGAAACA
GTGAGTTTGTCTGTACCATTAGGAGTTAGGTACTAATTAGTTGGCTAATGCTCAAGT
ATTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTCCCAGGACATCCACCCTGA
GAATAATTTGACAAGCTTAAAAATGGCCTTCATGTGAGTGCCAAATTTTGTTCCTTC
ATTTAAATATTTTCTTTGCCTAAATACATGTGAGAGGAGTTAAATATAAATGTACAGAG
AGGAAAGTTGAGTTCCACCTCTGAAATGAGAATTACTTGACAGTTGGGATACTTTAATC
AGAAAAAAGAACTTATTTGCAGCATTTTATCAACAAATTTTCATAATTGTGGACAATTG
GAGGCATTTATTTTAAAAACAATTTTATTGGCCTTTTGCTAACACAGTAAGCATGTAT
TTTATAAGGCATTCAATAAATGCACAACGCCCAAAGGAAATAAAATCCTATCTAATCC
TACTCTCCACTACACAGAGGTAATCACTATTAGTATTTTGGCATATTATCTCCAGGTGT
TTGCTTATGCACTTATAAAATGATTTGAACAAATAAACTAGGAACCTGTATACATGTG
TTTCATAACCTGCCTCCTTTGCTTGGCCCTTTATTGAGATAAGTTTTCTGTCAAGAAAG
CAGAAACCATCTCATTCTAACAGCTGTGTTATATTCCATAGTATGCATTACTCAACAA
ACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGACAATACTGAATAACATCT
CACCGGAATTC

Figure 104

MFLSILVALCLWLHLALGVRGAPCEAVRIPMCRHMPWNITRMPNHLHHSTQENAILAIEQY
EELVDVNCSAVLRFFFCAMYAPICTLEFLHDPIKPKSVCQRARDDCEPLMKMYNHSWPES
LACDELPVYDRGVCISPEAIVTDLPEDVKWIDITPDMMVQERPLDVDCKRLSPDRCKCKKV
KPTLATYLSKNYSYVIHAKIKAVQRSGCNEVTTVVDVKEIFKSSSPIRPTQVPLITNSSCQCP
HILPHQDVLIMCYEWRSRMMLLENCLVEKWRDQLSKRSIQWEERLQEQRRTVQDKKKT
GRTSRSNPPKPKGKPPAPKPASPKNKTRSAQKRTNPKRV

66/66

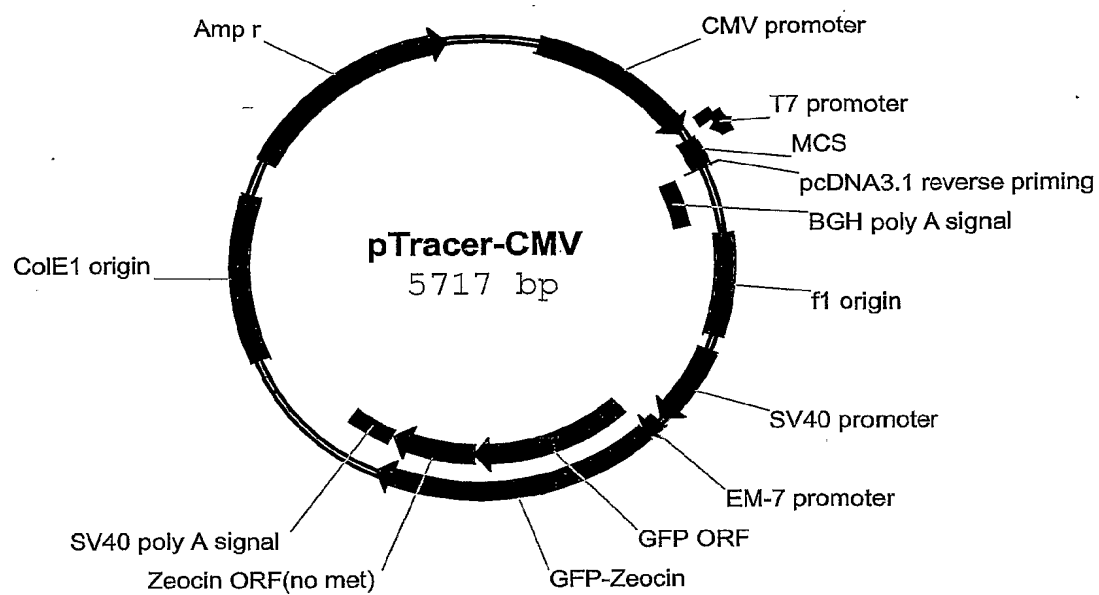


Figure 105